

Electron-Spin Resonance Studies of Nitroxide Radicals

Structure and Mechanism of Formation of the Radicals Formed From Tetranitromethane and 2-Monosubstituted 1,3-Dicarbonyl Compounds

CARL LAGERCRANTZ

Department of Medical Physics, University of Göteborg, Fack, S-400 33 Göteborg 33, Sweden

and

KURT TORSSELL

Institute of Organic Chemistry, University of Stockholm, Sandåsg. 2, S-113 27 Stockholm, Sweden

Reaction between tetranitromethane (TNM) and 2-monosubstituted 1,3-dicarbonyl compounds, $R'CO-CHR''-COR''$, produced symmetric nitroxide radicals, $[(R'CO)(R''CO)R''C]_2NO\cdot$. The ^{14}N splittings were about 13 gauss and the g -values about 2.0060. The structure of the radicals was settled from the secondary splittings of the radical obtained with TNM and diethyl acetamidomalonate, and by analysis of the spectra of the unsymmetric nitroxide radicals, $[(R'CO)(R''CO)R''C]-NO\cdot-[C(COCH_3)(CH_3)_2]$, formed by irradiation with light of a mixture of 1,3-dicarbonyl compounds, TNM or Ce^{4+} ions, and the stable nitroso compound, 2-methyl-2-nitrosobutanone-3 (III).

The mechanism of formation is shown to involve an oxidation of the 1,3-dicarbonyl compound to the radical, $R'CO-\dot{C}R''-COR''$ (IV) by TNM or Ce^{4+} ions. The radical (IV) then couples with a nitroso compound to form the nitroxide radicals. In the case of the symmetric nitroxide radicals an intermediate nitroso compound (I) is formed by the reaction of TNM with the 1,3-dicarbonyl compound. The action of radiant energy in the reactions leading to unsymmetric nitroxide radicals (V) involves a splitting of the dimeric state of the added nitroso compound (III).

Stable 2-iminoxy-1,3-dicarbonyl radicals, $R'CO-C(=NO\cdot)-COR''$, are formed by nitrosation of 1,3-dicarbonyl compounds, $R'CO-CH_2-COR''$, with tetranitromethane (TNM).¹ The ESR-spectra are dominated by a triplet

Table 1. Symmetric nitroxide radicals formed from 2-monosubstituted 1,3-dicarbonyl compounds and TNM.

Parent substance	Solvent	g -value	a^N gauss	Secondary split- tings gauss
1. 3-Methylpentanedione-2,4	Methanol-pyridine 1:1		13.2	—
2. 3-Ethylpentanedione-2,4	»		12.7	—
3. 3-Butylpentanedione-2,4	»		13.0	—
4. 3-Phenylpentanedione-2,4	»		13.1	—
5. 3- <i>p</i> -Tolylpentanedione-2,4	»		13.1	—
6. Diethyl methylmalonate	»	2.0060	13.6	—
7. Diethyl phenylmalonate	»		13.2	—
8. Diethyl acetamidomalonate	Methanol-pyridine 3:1		13.1	Quintet: $a^N = 1.6$
9. Methyl 2-methyl-3-oxoundecanoate	Methanol-pyridine 1:1		13.4	—
10. Ethyl 2-methyl-3-oxo-3-phenylpropanoate	»		13.7	—
11. 5-Ethylbarbituric acid	DMSO ^a	2.0066	11.9	Incompletely resolved multiplet
12. 5-Methylthiobarbituric acid	»		12.3	»
13. 5-Ethyl- <i>N</i> -methylbarbituric acid	»		11.9	»
14. 2-Methylcyclohexanedione-1,3	»	2.0062	12.6	At least 9 lines: $a^H \sim 0.4$
15. 2,5,5-Trimethylcyclohexanedione-1,3	»		13.1	Incompletely resolved multiplet
16. 2-Benzylcyclohexanedione-1,3	»		12.7	—
17. 4-Butyl-1,2-diphenyl-3,5-pyrazolidinedione (Butazolidine [®])	»		12.0	—

^a The radicals can also be produced in methanol-pyridine.

splitting in the range between 27 and 35 gauss originating from an interaction of the odd electron with the ¹⁴N nucleus of the iminoxy group.

When 2-monosubstituted 1,3-dicarbonyl compounds, R'CO—CHR'''—COR'', dissolved in methanol or dimethyl sulphoxide (DMSO), are reacted with TNM in the presence of a small amount of alkali or pyridine, stable free radicals are formed exhibiting a ¹⁴N triplet with a splitting constant, a^N , of about 13 gauss (Table 1) and a g -value of about 2.0060. No secondary splittings are resolved with aliphatic 1,3-dicarbonyl compounds if the substituent R''' is an alkyl or aryl group. Cyclic 2-monosubstituted 1,3-dicarbonyl compounds give rise to radicals with a number of more or less completely resolved secondary splittings (Fig. 1). The 2-alkyl substituted compounds give a higher yield of radicals than the 2-aryl substituted ones. The ESR-spectra of the radicals of this series exhibited the line-width variation due to anisotropy of the electronic g and nuclear hyperfine tensors with a broadening of the high-field component of the ¹⁴N triplet (to the right in the spectra).

We suspected that the spectra originated from nitroxide radicals, as such radicals exhibit a main ¹⁴N triplet splitting in the range of 9–15 gauss, and

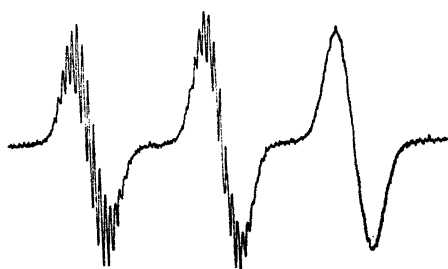


Fig. 1. ESR-spectrum of the nitroxide radicals formed in the reaction between TNM and 5-methylthiobarbituric acid.

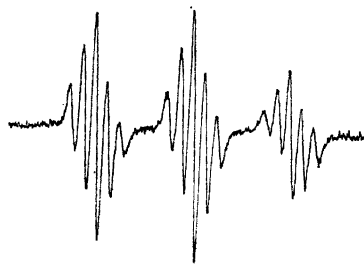
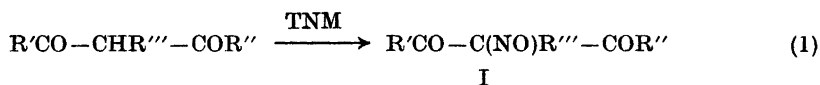


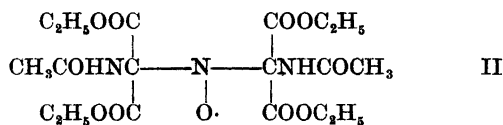
Fig. 2. ESR-spectrum of the nitroxide radicals formed in the reaction between TNM and diethyl acetamidomalonate.

g -values in the range between 2.0050 and 2.0070.²⁻⁶ From the chemical point of view it is conceivable that the initial reaction is a nitrosation, eqn. (1)



Evidence for the nitroxide structure was obtained as follows. In order to obtain interpretable secondary splittings, and thereby more information about the radicals of this series, it seemed necessary to use a parent 1,3-dicarbonyl compound of such a structure that the radicals formed would be carrying magnetic nuclei very close to the ^{14}N nucleus responsible for the main interaction.

Diethyl acetamidomalonate was thought to be a convenient test substance for our purpose. When dissolved in methanol-pyridine (3:1 v/v) containing a small amount of alkali, it gave rise to free radicals after addition of TNM. The ESR-spectrum exhibited the expected 3×5 line structure, Fig. 2. Each of the lines of the main triplet was further split into a quintet with the intensity ratio nearly equal to 1:2:3:2:1 due to an interaction with two equivalent ^{14}N nuclei, evidently those of the acetamido-group of two parent molecules (Table 1). These findings are consistent with structure II



Alternatively, the nitrosation might take place on the nitrogen atom of the amide group with the formation of the isomeric nitroxide radical. In case of such a structure we might expect that secondary amides would give rise to analogous radicals when reacted with TNM. However, no radicals could be detected with substances such as acetanilide and phthalimide. Therefore, structure II seems to be the more probable one. The stability of radical II was lower than that of the other radical species of this series.

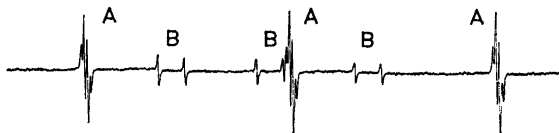
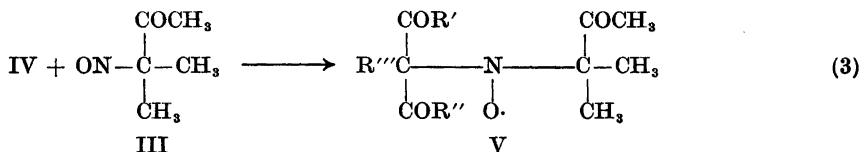
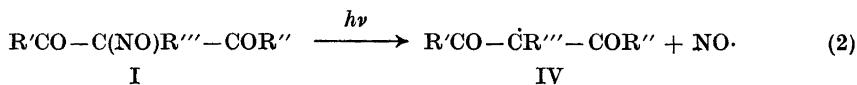


Fig. 3. ESR-spectrum of the radicals present in the reaction mixture of III and TNM + pentanedione-2,4.

A. iminoxy radicals derived from pentanedione-2,4.

B. nitroxide radicals formed in the cross-coupling reaction between III and TNM + pentanedione-2,4.

On the basis of mechanisms for the formation of nitroxide radicals from nitroso compounds on irradiation with light^{4,5} and eqn. (1) some cross-coupling reactions were designed which should confirm the nitroxide structure. Irradiation of a mixture of an added nitroso compound (2-methyl-2-nitrosobutanone-3, III), a 1,3-dicarbonyl compound and TNM was anticipated to give an unsymmetric nitroxide radical V, eqns. (2) and (3).



Alternatively, light could split III which then reacts with I giving V. If $\text{R}'''=\text{H}$, we should obtain in addition to the spectrum of the iminoxy radical (from the rearranged nitroso compound¹) a spectrum of V with the main triplet split into doublets by one hydrogen atom. In fact pentanedione-2,4 or methyl acetoacetate did give the anticipated spectrum, Fig. 3. Furthermore, it was possible to dissociate the proton by careful addition of base whereby the 3×2 line spectrum was transformed into a 3×1 line spectrum. The analogous spectrum was obtained with acetoacetanilide. In this case the secondary doublets were further split into triplets by the nitrogen nucleus of the amide group, Fig. 4. Cross-coupling of III with diethyl acetamidomalo-



Fig. 4. ESR-spectrum of the nitroxide radicals formed in the cross-coupling reaction between III and TNM + acetoacetanilide.



Fig. 5. ESR-spectrum of the nitroxide radicals formed in the cross-coupling reaction between III and TNM + diethyl acetamidomalonate.

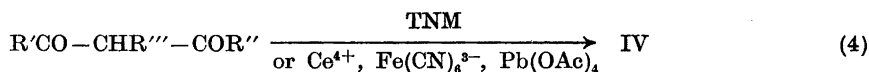
Table 2. Unsymmetric nitroxide radicals formed by cross-coupling between 1,3-dicarbonyl compounds and 2-methyl-2-nitroso-butanone-3 (III).

Parent substance	Solvent	g -value	a^N gauss	Secondary split- tings gauss
1. Pentanedione-2,4	Methanol	2.0060	13.2	Doublet: $a^H=3.53$
2. Methyl acetoacetate	»		13.3	Doublet: $a^H=3.76$
3. Acetoacetanilide	DMSO	2.0060	13.5	Doublet: $a^H=4.71$ Triplet: $a^N=0.61$
4. Diethyl acetamidomalonate	Methanol-pyridine 3:1		13.5	Four lines: $a\sim 0.2$

nate and TNM gave the expected unsymmetric nitroxide exhibiting secondary splittings from one amide group, Fig. 5.

The unsymmetric nitroxide radicals formed by cross-coupling with III are collected in Table 2. Irradiation of a solution of III without the presence of other substances produced the symmetric nitroxide radical $[(CH_3)_2(COCH_3)C]_2NO$ ($a^N=14.3$ gauss, $g=2.0060$), eqns. (2) and (3), I=III, the spectrum of which in most of the cross-coupling reactions did not obscure the spectrum of the unsymmetric radicals.

However, one has to consider another action of TNM, *i.e.* a direct oxidation of the 1,3-dicarbonyl compound to IV, eqn. (4)



As a matter of fact, this mechanism was found to be working, as we found that TNM could be replaced by other oxidizing reagents. Thus, the unsymmetric nitroxide radical exhibiting the 3×2 line system (Fig. 3) was produced by irradiation of a solution of pentanedione-2,4 and III in methanol or acetic acid after the addition of Ce^{4+} , $Fe(CN)_6^{3-}$ ions or lead tetraacetate. However, TNM was found to be the most efficient oxidizing reagent, giving the highest yield of radicals in our case. The formation of radicals according to eqn. (4) is consistent with the results obtained when oxidizing 2-methyl-1,3-cyclopentanedione by ceric ions.⁷ In this experiment radicals were observed by the aid of a flow system.

TNM has a twofold action in the reaction leading to the symmetric nitroxide radicals. It nitrosates the 1,3-dicarbonyl compound, eqn. (1), and oxidizes a second molecule to the radical IV, eqn. (4), which is trapped by the nitroso compound, eqn. (3), III=I.

Once the nitroso compound I derived from unsubstituted 1,3-dicarbonyl compounds has rearranged into the oxime,¹ no nitroxide radicals can be formed, as found when irradiating a solution of III and the 3-oxime derivative of pentanedione-2,4.

The reason that the radical IV does not couple with III without irradiation, is found in the fact that III is present mainly as a dimer at room temperature.⁸ The action of radiant energy involves a splitting into the active monomeric form. The dissociation of the colourless dimer into the blue monomer can also be produced by heating a solution of III in ethanol at the boiling point. After cooling to room temperature the monomer does exist for some minutes as evidenced by the persistence of the blue colour. When such a solution of III was used for the cross-coupling with pentanedione-2,4 and TNM, an ESR-spectrum identical to that of Fig. 3 was obtained.

Nitrosobenzene, which is present as a monomer in solution of methanol or acetic acid at room temperature, could also be used for cross-coupling with the radical IV formed by oxidation of pentanedione-2,4, or diethyl methylmalonate, by TNM or Ce^{4+} ions, respectively. In this case the unsymmetric nitroxide radicals were formed without any irradiation or pre-heating of the nitroso solution. However, the interpretation of the secondary splittings is seriously hampered by the presence of incompletely resolved splittings originating from the aromatic protons. This complication is precluded with the nitroso substance III which did not contribute to the secondary splittings of the unsymmetric nitroxide radicals.

EXPERIMENTAL

The ESR-spectra were obtained at room temperature with a Varian 100 kc spectrometer and a 9" magnet. Estimation of g -values was made for some radical species by use of the superposition spectrum obtained from a solution simultaneously containing the symmetric nitroxide radical derived from III and the p -benzosemiquinone radical ($g=2.00468$) as described earlier.¹ The g -value of a particular nitroxide radical was then obtained from superposition spectra of solutions simultaneously containing the nitroxide radical derived from III.

The irradiation experiments were performed *in situ*. The light-source was a high-pressure mercury lamp (Osram HBO-200).

The radicals were prepared by dissolving the substances in the appropriate solvent, adding TNM and a small amount of 1 M NaOH in H_2O . The radicals derived from the cyclic 2-monosubstituted 1,3-dicarbonyl compounds were produced without any addition of alkali when dissolved in DMSO containing a very small amount of pyridine.

Many of the compounds used were commercial preparations which were used as supplied or after purification. 2-Methyl-2-nitroso-butanone-3 (III) was prepared as described by Aston *et al.*⁸

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