ESR Study of *N*-Acyl-*N*-Alkyl Nitroxide Radicals from Photolysis of *N*-Nitrosoamides

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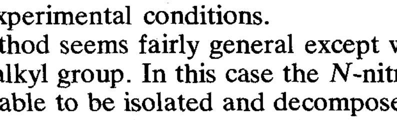
A new method of generation of *N*-acyl-*N*-alkyl nitroxide radicals by photolysis of *N*-nitrosoamides is described. ESR parameters are reported for 17 radicals of the general formula R—CO—N(R′)O˙; the high resolution obtained allows conformational analysis which shows a preferred *trans* conformation around the CO—N bond and hindered rotation around the N—R′ σ-bond.

N-acyl-*N*-alkyl nitroxide radicals of the general formula R—CO—N(R′)O˙ in which R′ is an alkyl group have never been thoroughly studied because of the lack of a sufficiently general method for varying the R′ substituent. De Boer and co-workers were able to generate some of these radicals by a spin trapping reaction during the photolysis of alkyl nitrites.[1] The ESR spectra obtained in this way seldom show good resolution because of the relatively large line widths. Furthermore the number of possible R′ substituents seems very limited. Other workers obtained such nitroxide radicals by oxidation of the corresponding *N*-hydroxyamides,[2,3] but this method still lacks generality because the synthesis of the starting compounds is difficult.

We wish to report here a very simple method which makes this class of nitroxide radicals readily available.

Generation of *N*-acyl-*N*-alkyl nitroxide radicals

We observed that low temperature photolysis of *N*-nitrosoamides in toluene solution gave rise to well resolved ESR spectra attributed to the corresponding nitroxide radicals on the basis of their hyperfine coupling constants and *g* values:



$$R{-}C(=O){-}N(NO){-}R' \xrightarrow{h\nu} R{-}C(=O){-}N(O^{\cdot}){-}R'$$

(When the present work was published as a preliminary note[4] we misinterpreted the ESR spectra, assigning them to amido radicals; since then Danen and Gellert[5] showed unambiguously that we were, in fact, dealing with nitroxide radicals.)

Figure 1 shows the resolution obtainable by the use of these experimental conditions.

This method seems fairly general except when R′ is a tertiary alkyl group. In this case the *N*-nitrosoamide is too unstable to be isolated and decomposes through rearrangement to a diazoester, as shown by White.[6]

The mechanism by which the *N*-nitrosoamide leads to the nitroxide radical is not completely clear, but dissolved oxygen or nitrogen oxides (particularly NO) seem to play some role because thorough degassing of the sample by several freeze–pump–thaw cycles strongly decreases the nitroxide concentration during ESR experiments.

A striking analogy is found in the chemistry of C-nitroso compounds which react with nitric oxide to give alkoxy radicals.[7] The complexity of nitric oxide containing systems is well established [7]and this point is substantiated by the following observation. Photolysis of a toluene solution of an *N*-nitrosoamide at low temperature (e.g. −90 °C) gives rise to the spectrum of the corresponding nitroxide radical. Cutting off the light produces a small increase in the nitroxide concentration. At this stage, if the temperature of the sample is raised (e.g. to −80 °C or more), the concentration of the radical rapidly increases. If the temperature is now decreased, the concentration of the radical decreases. Several such increase–decrease cycles may be realized on the same sample by varying the temperature correctly, provided that the sample has been photolyzed once. Thorough degassing seems to affect the magnitude of the concentration increase but does not suppress it; it is therefore difficult to conclude what is responsible for this behaviour (dissolved oxygen, dissolved nitrogen oxides, nitric oxide formed during photolytic cleavage of the N—NO bond of the *N*-nitrosoamide, or a combination of these factors).†

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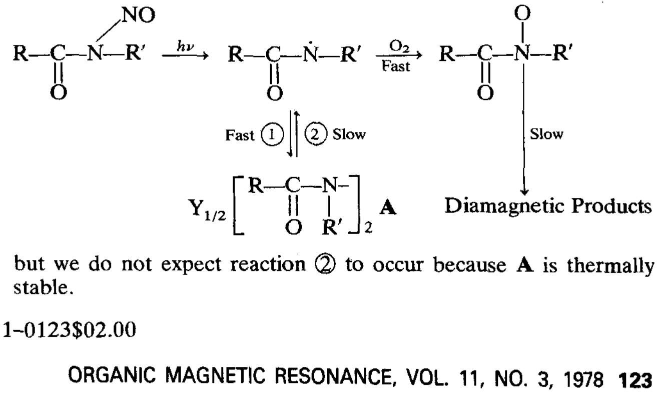
†One of the referees has suggested that these temperature effects are indicative of a reversible equilibrium such as



but we do not expect reaction ② to occur because **A** is thermally stable.

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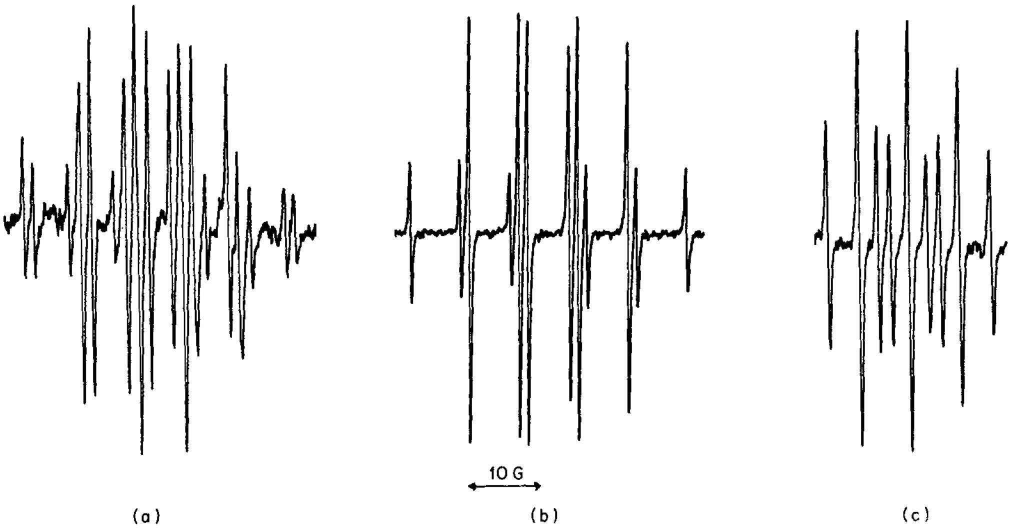


Figure 1. ESR spectra of some *N*-acyl-*N*-alkyl nitroxides: (a) *N*-formyl-*N*-methyl nitroxide **1** at −90 °C; (b) *N*-acetyl-*N*-methyl nitroxide **2** at −90 °C; (c) *N*-acetyl-*N*-benzyl nitroxide **10** at −70 °C.

To our knowledge, this light-induced self-catalyzed decomposition of *N*-nitrosoamides into nitroxide radicals has never been reported previously and deserves further investigation in order to establish its importance during photolysis of *N*-nitrosoamides.

ESR results

The spectral features of the observed nitroxide radicals R—CO—N(R′)O˙ obtained by photolysis of the corresponding *N*-nitrosoamides in toluene solution are listed in Table 1.

Table 1. ESR data for R—CO—N(R′)O˙ radicals

Number	Radical R	Radical R′	a_N(G)[a]	a_H(G)[a]	g	T (°C)[d]
1	H	CH_3	6.1	7.83(3H) 1.4 (1H)	2.0068	−90
2	CH_3	CH_3	6.9	8.1 (3H)	2.0066	−65
3	CH_3	CH_3CH_2	6.85	6.1 (2H)		−60
4	CH_3	$(CH_3)_2CH$	6.95	2.3 (1H)	2.0066	−60
5	CH_3	$(CH_3)_3C$	7.25[b]			−20
6	CH_3	$CH_3(CH_2)_2$	6.8	5.5 (2H)	2.0067	−70
7	CH_3	$CH_3(CH_2)_3$	6.77	5.5 (2H)		−70
8	CH_3	$CH_3(CH_2)_5$	6.77	5.5 (2H)	2.0066	−70
9	CH_3	$CH_2{=}CH{-}CH_2$	6.9	5.2 (2H) 0.1 (1H)	2.0066	−65
10	CH_3	$C_6H_5{-}CH_2$	6.9	4.4 (2H)	2.0068	−50
11	CH_3	cyclohexyl	6.83	2 (1H)	2.0067	−70
12	cyclohexyl	CH_3	6.95	8.1 (3H)	2.0065	−65
13	cyclohexyl	CH_3CH_2	6.92	6 (2H)		−80
14	cyclohexyl	$(CH_3)_2CH$	6.95	2.3 (1H)	2.0067	−80
15[c]	$-(CH_2)_5-$		7	4.4 (2H)	2.0065	−75
16[c]	$-(CH_2)_7-$		7	4.4 (2H)	2.0066	−40
17	$CHCl_2$	CH_3	5.7	7 (3H)	2.0070	−50

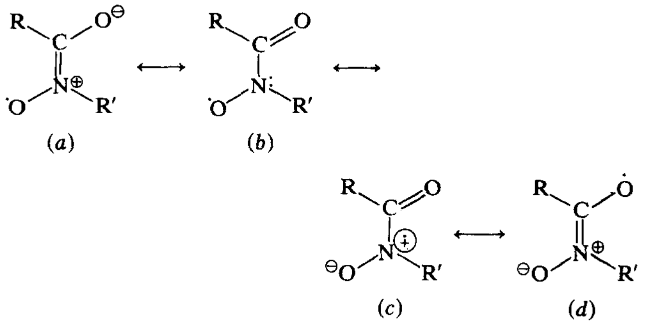
[a] a_N and a_H values are uncorrected i.e. the spectra were not calibrated by comparison with a stable free radical such as Frémy's salt.

[b] *N*-nitroso-*N*-tert-alkylamides are very unstable. The spectrum was obtained from samples showing signs of appreciable decomposition, which may explain the slightly different a_N value for the nitroxide radical.

[c] Obtained from the parent *N*-nitrosolactam.

[d] The temperature has no significant effect on the a_N, a_H, and g values.

The nearly constant a_N value for nitroxides **2–14** shows that these radicals have essentially the same electronic structure. Only an important modification of a substituent induces a significant change in the a_N value, for example in radicals **1** and **17** which show a reduced a_N value as expected from the lower electron-donor character of a hydrogen atom, or a dichloromethyl group, relative to an alkyl group. This may be rationalized by a decreased importance of mesomeric form (*c*).



This suggests that the CO—N bond must have some double bond character in all the *N*-acyl-*N*-alkyl nitroxides studied. This is in close agreement with the results of Perkins *et al.*[8] who carried out MO calculations on the simple formyl nitroxide H—CO—NHO˙ and found it to be planar in its ground state.

Stability of *N*-acyl-*N*-alkyl nitroxides

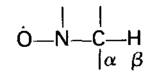
The ESR spectra obtained in these experiments generally have high signal-to-noise ratios, which means that the nitroxide concentrations are high. Because of the temperature effect we have just discussed, however, it is difficult to say whether this is due to the intrinsic stability of the observed nitroxides or to their continuous thermal generation. However, it seems that the stability of these radicals is strongly dependent on their structure. Those bearing a secondary alkyl group

Table 2. Spectral features of some secondary radicals formed from the primary nitroxides of Table 1

Primary nitroxide	Secondary nitroxide			
	a_N(G)[a]	a_{H_β}(G)[a, b]	*g*	*T* (°C)
2	6.75	4 (2H)	2.0067	0
6	6.93	2.66(1H)		0
7	6.85	2 (1H)		−20
10	7.05	2.65(1H)	2.0066	10
13	7	2.9 (1H)		−10

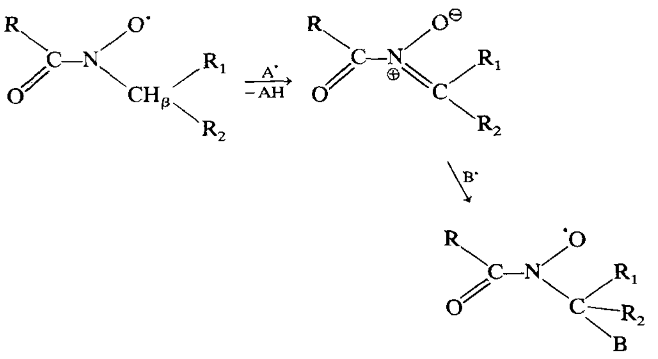
[a] a_N and a_{H_β} values are uncorrected. [See footnote a of Table 1].

[b] β-hydrogen atoms are labelled using the usual convention,



on the nitrogen atom (nitroxides **4, 11, 14**) are easily observed at temperatures as high as 40 °C or more. On the contrary, those bearing a primary or a methyl group begin to disappear at about −30 °C while another radical appears. This secondary species is also an *N*-acyl-*N*-alkyl nitroxide, as shown by its ESR parameters (Table 2).

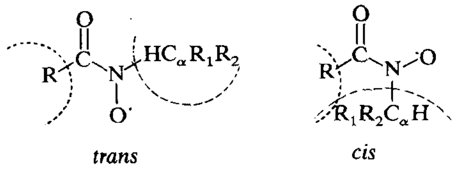
It can be easily observed that the secondary radical has one β-hydrogen atom less than that of the primary. It is reasonable to assume that the former is derived from the latter and the following scheme can account for these results.



In this proposed mechanism A˙ and B˙ are radicals present in the reaction mixture (eventually A˙ = B˙). Such a process, particularly the first step, would be favoured when $R_1 = R_2 = H$ or $R_1 = H$, R_2 = alkyl and would be more difficult when R_1 and R_2 are alkyl groups because of increased steric hindrance; this reflects closely the following trend of increasing stability, $Me_2NO^\cdot < Et_2NO^\cdot < (i\text{-}Pr)_2NO^\cdot$ found in dialkyl nitroxides.[12]

Cis-trans isomerism of *N*-acyl-*N*-alkyl nitroxides

By analogy with secondary amides it is reasonable to assume that the *trans* conformation is the most stable in *N*-acyl-*N*-alkyl nitroxides as it minimizes the steric interactions between R and the alkyl substituent $C_\alpha HR_1R_2$ of the nitrogen atom. A modification of R in the *trans* isomer is expected to have no effect on the $C_\alpha HR_1R_2$ substituent, whereas in the *cis* isomer it will induce a dramatic change in the populations of the different rotamers around the $N-C_\alpha$ bond, thus producing a variation in the H_β hyperfine splitting. Our results show that for the same $C_\alpha HR_1R_2$ substituent, on going from R = methyl to R = cyclohexyl (nitroxide pairs **2** and **12**, **3** and **13**, **4** and **14**) there is no significant effect on the a_{H_β} value or on the other spectral parameters.



We therefore conclude that *N*-acyl-*N*-alkyl nitroxides are essentially in a *trans* conformation. Even with *N*-formyl-*N*-methyl nitroxide **1** we have been unable to observe the two isomers simultaneously, whereas it is known that *N*-methylformamide contains about 8% of *cis* isomer.[9]

Hindered rotation around the σ N—C$_\alpha$ bond

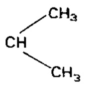
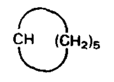
If we consider the a_{H_β} values for selected *N*-acetyl-*N*-alkyl nitroxides $CH_3—CO—N(R')O^\cdot$ as a function of the R′ group, an interesting feature appears (Table 3). a_{H_β} decreases with increasing steric hindrance around the C_α carbon atom. Such a trend has been observed for dialkyl nitroxides and Rassat *et al.*[10] and Janzen[11] have given very detailed discussions on this point. Their conclusions are still valid in the present case and it may be inferred that the most stable rotamers are those which have a β-atom close to the nodal plane of the odd electron π-type orbital. Furthermore when the C_α carbon is substituted by one or two alkyl groups, greater stabilization is found when a β-hydrogen atom rather than a carbon one lies close to the nodal plane.

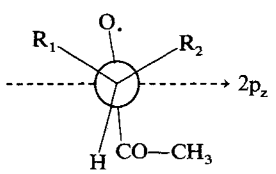
For example, in the case of *N*-acetyl-*N*-isopropyl nitroxide the most stable rotamer could be a_1 or b_1. The other preferred, though less populated, rotamers result from ±120° rotations of the isopropyl group around the N—C$_\alpha$ bond.

In the same manner, for *N*-acetyl-*N*-ethyl nitroxide the most stable conformation could be a_2 or b_2.

It is obviously impossible to make a choice between the s-*anti* and s-*syn* conformers purely from the ESR results.

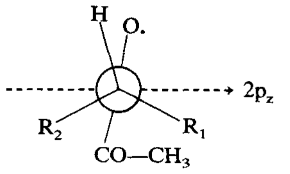
Table 3. H$_\beta$ hyperfine couplings for selected *N*-acetyl-*N*-alkyl nitroxides CH$_3$—CO—N(R′)O˙

R′	CH_3	$CH_2—CH_3$	$CH_2—CH_2—CH_3$		
a_{H_β}(G)	8.1	6.1	5.5	2.3	2



s-*anti*

a_1: $R_1 = R_2 = CH_3$
a_2: $R_1 = CH_3$
$R_2 = H$



s-*syn*

b_1: $R_1 = R_2 = CH_3$
b_2: $R_1 = CH_3$
$R_2 = H$

CONCLUSIONS

A general and convenient method for obtaining *N*-acyl-*N*-alkyl nitroxides for ESR studies has been developed which is based on photolysis of the readily available *N*-nitrosoamides. A systematic study of nitroxides generated in this way led us to the conclusion that these radicals exist essentially as the *trans* isomers, in agreement with the corresponding secondary amides. Finally the dependence of the a_{H_β} coupling on substitution at the C_α carbon atom is well explained by hindered rotation of the nitrogen substituent around the N—C_α bond, with preferred rotamers possessing a C_α—H_β bond lying close to the nodal plane of the singly occupied π-orbital.

EXPERIMENTAL

Compounds

Nitrosation of the amides was accomplished according to known procedures;[6] *N*-nitrosoamides were vacuum-distilled prior to use when their stability was sufficient, and characterized by classical methods (IR, UV, NMR).

When purification was not possible NMR showed that the principal impurity was unreacted amide, which is not troublesome in the photolysis step (except for *N*-nitroso-*N*-tert-butylacetamide where the sample contained several unidentified by-products due to the known instability of *N*-nitroso-*N*-tert-alkylamides). Thus either a purified *N*-nitrosoamide or a crude one, prepared by any of the methods studied by White,[6] gave identical ESR spectra.

Nitroxide radicals

These were generated by in situ photolysis of *N*-nitrosoamides in toluene (approximately 10% solution). Ultraviolet radiation was supplied by a water-cooled Philips SP 500 W lamp and focussed on the sample with quartz lenses.
The ESR spectrometer was a Varian E-3.

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Received 2 June 1977; accepted 10 September 1977.