

Oxidation of Substituted 3-Anilinopyrazoles with RO_2^\bullet Radicals, Studied by EPR Spectroscopy

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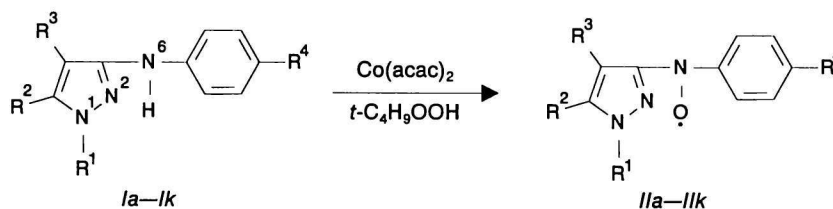
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The reaction of RO_2^\bullet radicals with substituted 3-anilinopyrazoles, containing different types of aminic groups in their molecule, proceeds under formation of nitroxyl radicals. Radical attack occurs preferentially on the exocyclic NH group. Under specific steric conditions nitroxyl radicals were observed as products of the oxidation of NH_2 group in the position 5 of pyrazole ring. No radicals coming from the oxidation of endocyclic NH group were identified. The studied nitroxyl radicals are characterized by their EPR parameters.

In our previous papers [1, 2] we have reported on the reaction of $t\text{-C}_4\text{H}_9\text{OO}^\bullet$ radicals with some substituted 3-anilinopyrazoles. Within the series of 3-anilino-1,5-diphenylpyrazoles [1] high-resolved EPR spectra of nitroxyl radicals were obtained. These radicals are formed by the oxidation of exocyclic NH group according to the mechanism proposed by Thomas [3]. The mentioned group represents the only active site for the attack of RO_2^\bullet radicals. The preliminary EPR experimental results of the oxidation of substituted 3-anilinopyrazoles containing more active sites in the molecule (exo- and endocyclic NH group, NH_2 group) have shown [2] that also in this case RO_2^\bullet radicals reacted preferentially with the exocyclic NH group. In order to evaluate in more detail structural conditions for the reaction of $t\text{-C}_4\text{H}_9\text{OO}^\bullet$ radicals with different aminic groups in the molecule of 3-anilinopyrazoles, further compounds of this type have been studied using EPR spectroscopy.

EXPERIMENTAL

3-Anilinopyrazoles *la–lm* were synthesized according to literature [1, 2, 4, 5].



<i>a</i>	$\text{R}^1 = \text{R}^3 = \text{R}^4 = \text{H}, \text{R}^2 = \text{NH}_2$
<i>b</i>	$\text{R}^1 = \text{R}^3 = \text{R}^4 = \text{H}, \text{R}^2 = \text{CH}_3$
<i>c</i>	$\text{R}^1 = \text{R}^3 = \text{R}^4 = \text{H}, \text{R}^2 = \text{C}_6\text{H}_5$
<i>d</i>	$\text{R}^1 = \text{R}^2 = \text{R}^4 = \text{H}, \text{R}^3 = \text{COOC}_2\text{H}_5$
<i>e</i>	$\text{R}^1 = \text{R}^4 = \text{H}, \text{R}^2 = \text{NH}_2, \text{R}^3 = \text{COOC}_2\text{H}_5$
<i>f</i>	$\text{R}^1 = \text{R}^4 = \text{H}, \text{R}^2 = \text{NH}_2, \text{R}^3 = \text{CN}$
<i>g</i>	$\text{R}^1 = \text{H}, \text{R}^2 = \text{NH}_2, \text{R}^3 = \text{CN}, \text{R}^4 = \text{CH}_3$

As a source of $t\text{-C}_4\text{H}_9\text{OO}^\bullet$ radicals the system $t\text{-C}_4\text{H}_9\text{OOH—Co(II) acetylacetonate}$ was used [6]. 3-Anilinopyrazoles *l* were oxidized using the following method: Compound *l* was dissolved in benzene solution of 5×10^{-2} M cobalt acetylacetonate in the mole ratio $n(l) : n(\text{Co}(\text{acac})_2) = 5 : 1$. To 2 cm³ of this solution *tert*-butyl hydroperoxide (TBHP) was added with stirring in the mole ratio $n(\text{TBHP}) : n(\text{Co}(\text{acac})_2) = 10 : 1$. Before the EPR measurements, argon was bubbled through the reaction mixture for a short time.

The EPR spectra were recorded with a Varian E-3 spectrometer, their simulation was carried out by using Aspect 2000 spectral computer.

RESULTS AND DISCUSSION

From the structural point of view, substituted 3-anilinopyrazoles (Scheme 1) *la–lh, lk–lm* can be considered as polyfunctional antioxidants. This results from the fact that theoretically each aminic group occurring simultaneously in the molecule can individually react with RO_2^\bullet and RO^\bullet radicals, respectively. For this reason, the formation of different types of nitroxyl radicals as main radical products from

<i>h</i>	$\text{R}^1 = \text{H}, \text{R}^2 = \text{NH}_2, \text{R}^3 = \text{CN}, \text{R}^4 = \text{Br}$
<i>i</i>	$\text{R}^1 = t\text{-C}_4\text{H}_9, \text{R}^2 = \text{CH}_3, \text{R}^3 = \text{R}^4 = \text{H}$
<i>j</i>	$\text{R}^1 = \text{R}^2 = \text{C}_6\text{H}_5, \text{R}^3 = \text{R}^4 = \text{H}$
<i>k</i>	$\text{R}^1 = \text{CH}_3, \text{R}^2 = \text{NH}_2, \text{R}^3 = \text{COOC}_2\text{H}_5, \text{R}^4 = \text{H}$
<i>l</i>	$\text{R}^1 = \text{C}_6\text{H}_5, \text{R}^2 = \text{NH}_2, \text{R}^3 = \text{R}^4 = \text{H}$
<i>m</i>	$\text{R}^1 = \text{C}_6\text{H}_5, \text{R}^2 = \text{NH}_2, \text{R}^3 = \text{H}, \text{R}^4 = \text{OCH}_3$

Scheme 1

Table 1. EPR Parameters of Nitroxyl Radicals // in Benzene

Radical	Splitting constant/mT						
	$a(N^6)$	$a(N^1)$	$a(N^2)$	$a(H^4)$	$a(H_o)$	$a(H_m)$	$a(H_p)$
<i>IIa</i>	0.940 ^a	—	—	—	—	—	—
<i>IIb</i>	0.960 ^a	—	—	—	—	—	—
<i>IIc</i>	0.990 ^a	—	—	—	—	—	—
<i>IId</i>	0.965	0.075	0.255	—	0.185	0.075	0.185
<i>IIe^b</i>	1.000	—	0.220	—	0.220	—	0.220
<i>IIf</i>	0.878	0.078	0.200	—	0.205	0.078	0.205
<i>IIg</i>	0.878	0.078	0.200	—	0.205	0.078	0.205 ^c
<i>IIh</i>	0.862	0.078	0.200	—	0.205	0.078	—
<i>IIi</i>	0.950	—	0.200	0.076	0.253	0.076	0.253
<i>IIj^d</i>	0.919	0.045	0.186	0.104	0.238	0.082	0.238
<i>IIk</i>	0.947	—	0.262	—	0.237	0.087	0.237

a) Further splittings unresolved; b) data from Ref. [2]; c) splitting by protons of CH₃ group; d) data from Ref. [1].

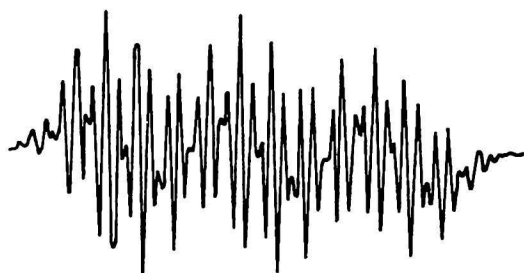
the oxidation of aminic group with RO₂^{*} radicals [3] can be expected. However, according to the experimental results, in the greater part of 3-anilino-pyrazoles studied the attack of RO₂^{*} radicals proceeds at the exocyclic NH group between pyrazole and benzene ring. Therefore, nitroxyl fragment —NO— is situated on the nitrogen atom N⁶ (Scheme 1).

Nitroxyl radicals // ($g = 2.0061$ — 2.0066) are characterized by the spin density distribution in both the benzene and pyrazole ring (Table 1). For radicals *IIe* and *IIf* the localization of radical centre was confirmed by experiments using ¹⁵N labeled compounds *le* and *lf* in the position 6. Unresolved EPR spectra of nitroxyls *IIa*—*IIc* allowed only the exact determi-

nation of basic nitrogen splitting $a(N^6)$. More pieces of information about spin density distribution were obtained from the EPR spectra of nitroxyls *IId*—*IIk*. In this case, splittings from *ortho* and *para* protons of the benzene ring (with the exception of *IIe* also *meta* protons) and nitrogen atom N² were accomplished. Lower values of splitting constant $a(N^6)$ for radicals *IIf*—*IIh* result from a considerable electron-accepting character of CN group in the position 4 of pyrazole ring (Fig. 1). Under our experimental conditions, no radicals were detected, which could be produced by the attack of RO₂^{*} radicals on endocyclic NH group. This statement is beyond any doubt in the case of those nitroxyls, where splittings with protons of benzene ring were demonstrated. In the case of nitroxyls with unresolved EPR spectra (*IIa*—*IIc*), the localization of a radical centre at the N⁶ atom is favoured by the $a(N^6)$ value. It is known [7—9] that basic nitrogen splitting of nitroxyls formed by the oxidation of endocyclic NH group in conjugated *N*-heterocyclic compounds is substantially lower and reaches the values of 0.4—0.7 mT. However, by the electrochemical oxidation of *IIe* dimeric products are formed [4] as a result of N—N coupling in the position 1 of pyrazole ring.

Unambiguous preference for attack of RO₂^{*} radicals in the position 6 was typical for all 3-anilino-pyrazoles mentioned above. Significant changes of EPR parameters occur in the case of oxidation of *IIl* and *IIm*. In contrast with radicals *IIa*—*IIk*, the detected nitroxyls ($g = 2.0063$) are characterized by spin density distribution only within the pyrazole ring, as

experimental



simulated

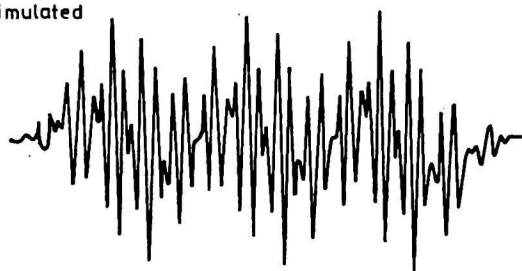
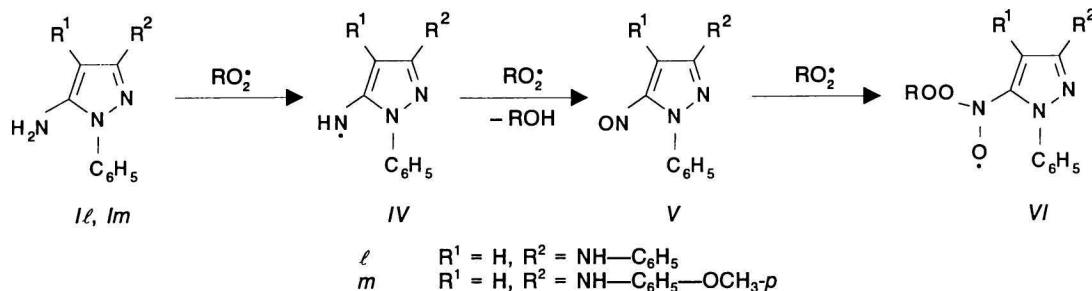


Fig. 1. Experimental and simulated EPR spectrum of the radical *IIj* in benzene.

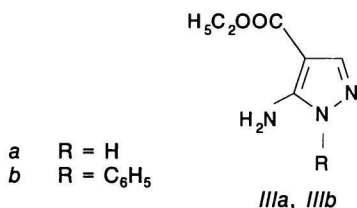


Fig. 2. EPR spectra of nitroxyl radicals generated from 3-anilino-pyrazole *IIl* (a) and substituted pyrazole *IIlb* (b).



Scheme 2

confirmed by splitting constant values (nitroxyl from *l*: $a(N) = 1.087$ mT, $a(N) = 0.125$ mT (2N), $a(H) = 0.200$ mT; nitroxyl from *lm*: $a(N) = 1.040$ mT, $a(N) = 0.162$ mT, $a(N) = 0.082$ mT, $a(H) = 0.175$ mT). It is evident that no characteristic splitting constants for protons of benzene ring were found (Fig. 2a). Since besides exocyclic NH group only NH₂ group in the position 5 is an active site for RO₂[•] radical attack, it is necessary to assume its efficient role in the oxidation of *l* and *lm*. The question arises, why NH₂ group is preferentially attacked by RO₂[•] radicals only under structural conditions of 3-anilinopyrazoles *l* and *lm*. The presence of benzene ring in the position 1 of pyrazole ring which represents specific steric factor for NH₂ group in its vicinity seems to be the most acceptable explanation of this phenomenon. In order to confirm this theory, substituted pyrazoles *lla* and *llb* were oxidized by the same procedure as with *la*–*lk*.



While no radicals were observed under laboratory temperature in the case of *lla*, compound *llb* affords nitroxyl radical (Fig. 2b) with the following splitting constants: $a(N) = 1.01$ mT, $a(N) = 0.173$ mT, $a(N) = 0.062$ mT, $a(H) = 0.062$ mT. It is evident that the reaction of RO₂[•] radicals with NH₂ group proceeds when this is sterically hindered by benzene ring. Interpretation of EPR spectra of nitroxyls from *l*, *lm*, and *llb* is based on the experimental fact that in addition to the splittings from three nitrogen atoms splitting from only one hydrogen atom ($a(H) \leq 0.2$ mT) was observed. Consequently, detected radical products of the oxidation of NH₂ group cannot be considered as heteroaryl nitroxyls X–N[•]O–H (X = pyrazole ring). These are namely characterized by higher values of splitting constant

of hydrogen atom attached to the nitroxyl group ($a(H) \approx 1.2$ mT) [10]. Therefore, it is supposed that in the series of subsequent reactions the complete oxidation of NH₂ group takes place. Photolytic EPR study of substituted anilines in the presence of di(*tert*-butyl) peroxide and *tert*-butyl hydroperoxide in benzene solutions presented by Danen *et al.* [11] proved the existence of arylalkoxy nitroxyls Ar–N[•]O–OR (R = *t*-C₄H₉) as the main radical products. Considering this fact, the formation of nitroxyls from *l* and *lm* can be described by the following mechanism (Scheme 2).

Oxidation of substituted pyrazole *llb* can be interpreted in the same way. In Scheme 2 radical VI is declared as the adduct of RO₂[•] radicals with nitroso compound V. Since the system Co(acac)₂–*t*-C₄H₉OOH produces not only RO₂[•] but also RO[•] radicals [12], the addition of *t*-C₄H₉O[•] radicals to V cannot be excluded.

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