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INVESTIGATION OF SHORT LIVED RADICALS IN AROMATIC NUCLEOPHILIC SUBSTITUTION BY USE OF NITROSO COMPOUNDS AS SCAVENGERS

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Abstract—Radical intermediates formed in reaction of substituted nitrobenzene compounds with nucleophilic reagents have been trapped by t-nitrosobutane to yield nitroxide radicals which have been characterized *in situ* by ESR. The formation of short-lived radicals originating from reagents and solvents has been shown.

The first step in aromatic[1-6] nucleophilic substitution was supposed to proceed as a one-electron transfer from the reagent to organic compounds.

$$\mathrm{RX} + \mathrm{Y}^- \rightarrow \mathrm{RX}^{\dot{+}} + \dot{\mathrm{Y}}. \qquad (1)$$

The radical mechanism of these reactions was confirmed by direct detection of the radical-anions of parent compounds by ESR[1-5] and by kinetic regularities of formation of radical-anions under different conditions.[3-5] Important evidence of the radical mechanism in nucleophilic substitution could be the detection and identification of short-lived free radicals originating from reagents.

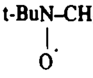
Recently,[7,8] the application of spin trapping as a diagnosis of short-lived free radicals has been observed. We have applied the nitroxide method[7-9] to trap short-lived radicals produced in reactions of substituted nitrobenzenes with nucleophilic reagents in different solvents. t-Nitrosobutane (t-BuNO) has been used as scavenger.

Reactions of aromatic nitro compounds with KOH *and* MeONa. Reactions of *p*-nitrochlorobenzene, *p*-nitroiodobenzene and *p*-dinitrobenzene with hydroxide and methoxide are typical of nucleophilic aromatic substitution. Therefore they are of interest for the study of the radical mechanism. ESR spectra of the stable radical **1** and radical-anions of *p*-nitrochlorobenzene or *p*-dinitrobenzene have been obtained in reactions of these three nitro compounds with potassium hydroxide in DMSO–H_2O (4:1 v/v) mixture in the presence of t-BuNO. The radical-anion of *p*-nitroiodobenzene is not stable.[10] For this reason further investigations have been carried out with *p*-nitroiodobenzene because its radical-anion does not mask the lines of nitroxide radicals.

The ESR spectrum of radical **1** exhibited a ^{14}N triplet (1:1:1) with secondary splitting from three equivalent protons to a quartet (1:3:3:1), $a_N = 16{\cdot}0$ g, $a_H = 13{\cdot}2$ g. The splitting constants are similar to those known[11] for radical **1**. The ESR spectra of radical-anions of parent nitro compounds are identical to known spectra.[12]

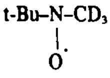
The stable radical **2** is formed, with DMSO-d_6–H_2O (4:1 v/v) mixture used as a solvent. The 3 × 7 line spectrum exhibited ^{14}N triplet with secondary splitting on three equivalent deuterium atoms in the ratio 1:3:6:7:6:3:1, $a_N = 15{\cdot}9$ g, $a_D = 2{\cdot}0$ g, which is in agreement with the data.[11]

In all these cases we have failed to show the formation of radical **3**. In the reaction with methoxide in DMSO–MeOH (1:10 v/v) at −70°, we observed the formation of radical **1**, radical-anion $t\text{-BuNO}^{\dot{-}}$ and a triplet (1:1:1), $a_N = 28$ g which is specific for alcoxynitroxide radicals[17] and probably belongs to radical **4**.



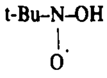
$$t\text{-BuN}(\dot{O})\text{–CH}_3$$

1



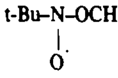
$$t\text{-Bu–N}(\dot{O})\text{–CD}_3$$

2



$$t\text{-Bu–N}(\dot{O})\text{–OH}$$

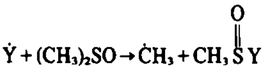
3



$$t\text{-Bu–N}(\dot{O})\text{–OCH}_3$$

4

The formation of radicals **1** and **4** can be demonstrated by reactions 1–4:



$$\dot{\mathrm{Y}} + (\mathrm{CH_3})_2\mathrm{SO} \rightarrow \dot{\mathrm{C}}\mathrm{H_3} + \mathrm{CH_3}\overset{\mathrm{O}}{\overset{\|}{\mathrm{S}}}\mathrm{Y} \qquad (2)$$

$$\dot{\mathrm{C}}\mathrm{H_3} + t\text{-BuNO} \rightarrow (1) \qquad (3)$$

$$\dot{\mathrm{O}}\mathrm{CH_3} + t\text{-BuNO} \rightarrow (4) \qquad (4)$$

$$\dot{\mathrm{Y}} = \dot{\mathrm{O}}\mathrm{H}, \dot{\mathrm{O}}\mathrm{CH_3}.$$

The probability of such a mechanism is confirmed by the data[11] on the formation of a Me-radical in the reaction of DMSO with hydroxyl-radical resulting from the decomposition of H_2O_2.

It is necessary to take into account the possibility of the formation of radical **4** in the reaction of methoxide with t-BuNO and further oxidation of amino-oxy-anion formed.[13]

The ESR spectrum of three nitroxide radicals was obtained in the reaction of *p*-nitroiodobenzene with hydroxide or methoxide in DMF (Fig 1). The parameters of one signal, a single ^{14}N triplet $a_N = 11{\cdot}8$ g is explained

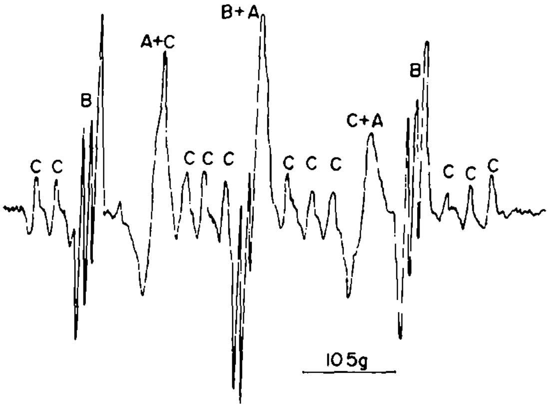
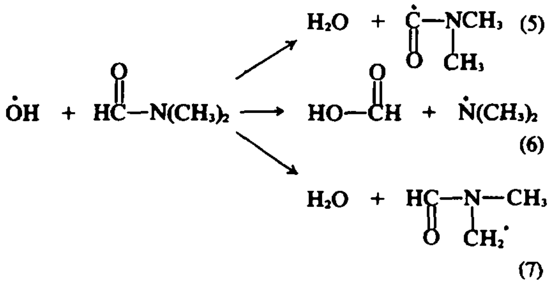


Fig 1. ESR spectra of Radicals obtained in reaction of p-iodonitrobenzene with potassium hydroxide in DMF in the presence of t-BuNO. The following nitroxides are present: A-(5); B-(6); C-(7).

by formation of radical **5**. In most cases splitting constants for acylnitroxides have the value $a_N = 7–8$ g.[9] But recently Perkins *et al.*[14] have found for radical **5** a splitting constant $a_N = 11{\cdot}75$ g, which is in good agreement with our data. They also observed a secondary splitting. In our case the line-width (Fig 1) indicates the presence of such a splitting. The ESR spectrum of the second radical (**6**) consists of 3 × 3 lines and exhibits main ^{14}N triplet of nitroxide nitrogen $a_{N(1)} = 18{\cdot}2$ g and further splitting into ^{14}N triplet of amine nitrogen $a_{N(2)} = 0{\cdot}69$ g.

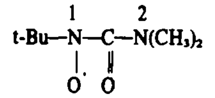
The ESR spectrum of third radical (**7**) is more complicated (Fig 2), $a_{N(1)} = 15{\cdot}0$ g, $a_{N(2)} = 2{\cdot}3$ g, $a^{CH_2}_{H(1)} = 18{\cdot}0$ g, $a^{CH_2}_{H(2)} = 0$. It can be explained if we assume that in radical **7** the rotation of the CH_2-group in the $\dot{O}$–N–CH_2 fragment around the N–C bond is hindered. This can lead to such nonequivalency of two methylene protons that the interaction of the unpaired electron can only occur with one of the two protons in the CH_2-group. The possibility of formation of the radical in question was discussed earlier.[8,15]

The formation of radicals **5–7** can be explained by the interaction of DMF with the hydroxyl-radical formed in reaction (1):



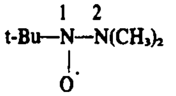
The reaction of p-nitroiodobenzene with methoxide in DMF proceeds in the same way.

Fig 2. ESR spectrum of Radical (7)



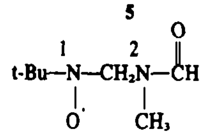
5

$$\text{t-Bu}-\underset{\text{O}^{\bullet}}{\overset{1}{\text{N}}}-\underset{\text{O}}{\overset{2}{\text{C}}}-\text{N(CH}_3)_2$$



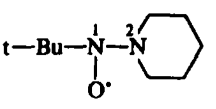
6

$$\text{t-Bu}-\underset{\text{O}^{\bullet}}{\overset{1}{\text{N}}}-\overset{2}{\text{N}}(\text{CH}_3)_2$$



7

$$\text{t-Bu}-\underset{\text{O}^{\bullet}}{\overset{1}{\text{N}}}-\text{CH}_2\overset{2}{\text{N}}(\text{CH}_3)-\text{CH=O}$$



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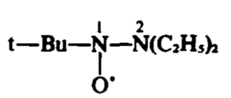
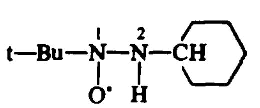


9

$$\text{t-Bu}-\underset{\text{O}^{\bullet}}{\overset{1}{\text{N}}}-\overset{2}{\text{N}}(\text{C}_2\text{H}_5)_2$$



10

The reaction of aromatic nitro compounds with amines. The investigation of reactions with uncharged reagents is of peculiar interest. In one-electron transfer reaction with such reagents one may expect the formation of a radical-cation:

$$RX + YH \rightarrow RX^{\dot{}} + YH^{\dot{+}}. \qquad (8)$$

We have studied the interaction of p-dinitrobenzene and picrylchloride with piperidine, diethylamine and cyclohexylamine in DMSO, DMF and benzene. These reactions yield radicals **8–10**. The ESR spectrum of the reaction of picrylchloride with piperidine in benzene shows a ^{14}N triplet with secondary splitting into a 1:3:4:3:1 quintet due to the amine ^{14}N and two equivalent protons, $a_{N(1)} = 18{\cdot}5$ g, $a_{N(2)} = 0{\cdot}89$ g, $a_H = 0{\cdot}89$ g (Fig 3). In the reaction of p-dinitrobenzene or picrylchloride with piperidine in DMSO the formation of radicals **8** and **1** is observed while in the reaction of picrylchloride with piperidine in DMF radicals **7** and **8** are obtained.

The formation of radical **8** can be described by the following equations:

$$RX + C_5H_{10}NH \rightarrow RX^{\dot{}} + C_5H_{10}NH^{+} \qquad (9)$$

$$C_5H_{10}NH^{\dot{+}} + C_5H_{10}NH \rightarrow C_5H_{10}N^{\dot{}} + C_5H_{10}NH_2^{+} \qquad (10)$$

$$C_5H_{10}N^{\dot{}} + \text{t-BuNO} \rightarrow (\mathbf{8}). \qquad (11)$$

The formation of a free aminyl-radical in basic media is known.[16] Radical $C_5H_{10}N^{\dot{}}$ reacts with DMSO and DMF according to Eqs (2) and (7).

The ESR spectrum of radical **9** formed in the reaction of picrylchloride with diethylamine in benzene exhibits only a ^{14}N triplet with splitting constant $a_{N(1)} = 17{\cdot}9$ which

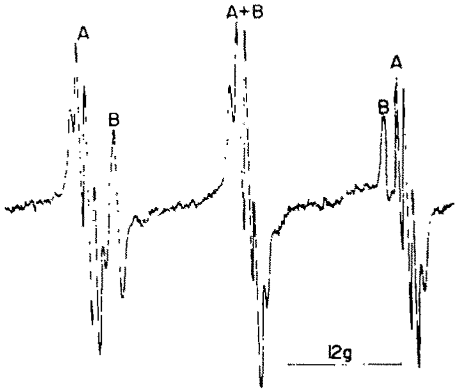


Fig 3. ESR spectra obtained in reaction of picrylchloride with piperidine in benzene in the presence of t-BuNO: A-(**8**); B-(**11**).

is less than that in radicals **6** and **8**. The splitting on N(2) or protons of methylene groups has not been observed. But the line width of this spectrum indicates a secondary splitting.

The spectrum of radical **10** is similar to that of radical **8**, $a_{N(1)} = 18{\cdot}6$ g, $a_{N(2)} = 0{\cdot}9$ g, $a_H{}^{NH} = 0{\cdot}9$ g, $a_H{}^{CH} = 0{\cdot}9$ g.

The reaction of t-BuNO *with nucleophiles.* t-BuNO reacts with hydroxide or alkoxides in methanol with formation of radical t-BuNO$^{\dot{-}}$, $a_N = 13{\cdot}8$ g. In a short time, a new triplet $a_N = 15{\cdot}9$ g appeared which is characteristic of the radical **11**. Its intensity increased while that of t-BuNO$^{\dot{-}}$ decreased. The addition of such solvents as DMF, DMSO to methanol accelerated this process. In pure DMF or DMSO the formation of radical t-BuNO$^{\dot{-}}$ has not been observed and radical **11** appears immediately after the addition of a reagent, e.g. piperidine. Such electron acceptors as picrylchloride, tetracyanethylene, chloroanyl, *p*-dinitrobenzene mainly hinder formation of radical **11**. The inhibition of formation of radical **11** can be explained by the reactions:

$$\text{t-BuNO} + \text{Y}^- \rightarrow \text{t-BuNO}^{\dot{-}} + \dot{\text{Y}} \qquad (12)$$

$$\text{t-BuNO}^{\dot{-}} \rightarrow \text{t-Bu}^{\cdot} + \text{NO}^- \qquad (13)$$

$$\text{t-BuNO} + \text{t-Bu}^{\cdot} \rightarrow \text{t-Bu}_2\text{NO}^{\cdot}\ (11) \qquad (14)$$

$$\text{t-BuNO}^{\dot{-}} + \text{RX} \rightarrow \text{t-BuNO} + \text{RX}^{\dot{-}}. \qquad (15)$$

When the concentration of t-BuNO is sufficiently high, the formation of radicals from the interaction of $\dot{\text{Y}}$ with solvents takes place. Therefore to exclude the possibility of the formation of nitroxides on account of reaction (12) the concentration of t-BuNO has been $10^2 - 10^3$ in all times less than that of substrates experiments described. Under these conditions in experiments without substrate the formation of radicals from reagents or solvents has not been observed. Consequently the appearance of such radicals by adding substrates is connected with the interaction of substrate and reagent (Eq 1). If the electron-withdrawing of the substrate is larger than that of t-BuNO (in reactions with *p*-dinitrobenzene and picrylchloride) formation of t-BuNO$^{\dot{-}}$ (Eq 15) is inhibited and this leads to regeneration of t-BuNO. In this case the formation of nitroxides may partially proceed due to reaction (12). But this is of no importance because the rate of reaction (1) is greater both because of the greater concentration and larger electron withdrawing of the substrate.

EXPERIMENTAL

The t-nitrosobutane was prepared by oxidation of t-butylhydroxylamine[17] with alkaline aqueous hypobromite solns.[18] The t-nitrosobutane was split into the monomeric state thermally. Other compounds used were commercial preparations and were used after purification. Solvents and reagents were purified by standard methods.

The radicals were prepared by dissolving the parent substance (0·1–0·2 M) together with the nitroso scavenger (10^{-3}–10^{-4} M) in the appropriate solvent and adding the reagent (0·2–0·4 M).

ESR spectra were measured on EPR-3 "Siberia" spectrometer employing 20 kc/s modulation at room temp. The hyperfine splitting was measured relatively to that of Fremy's salt ($a_N = 13{\cdot}09$ g).[19] The solns used were not de-airated.

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