

# **Free radicals in vicarious C-amination reactions of 1-methyl-4-nitropyrazole**

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The primary radical anions of substrate in the reactions of vicarious nucleophilic substitution of hydrogen in 1-methyl-4-nitropyrazole with 1,1,1-trimethylhydrazinium iodide and 4-amino-1,2,4-triazole in *t*-BuOK–DMSO were observed and identified by EPR monitoring. The probable mechanism of the substrate radical anions formation is discussed. Copyright © 2005 John Wiley & Sons, Ltd.

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### INTRODUCTION

The introduction of functional groups in nitroaromatic compounds via the reaction of vicarious nucleophilic substitution (VNS) of hydrogen<sup>1.2</sup> has greatly supplemented the arsenal of previously accessible azoles containing both nitro and amino groups.<sup>3</sup> In spite of many attempts to shed light on the mechanism of hydrogen VNS reactions,<sup>4–8</sup> the elementary stages of this process are still poorly understood. A universally adopted viewpoint in the literature is that the reaction proceeds through the polar mechanism involving the formation of intermediate  $\sigma^{\rm H}$ -complex.<sup>6</sup>

The VNS of hydrogen reactions requires some conditions favoring realization of redox process: the substrate should have a strong electron-withdrawing group (mostly  $NO_2$ ); strong basic media as a contributory factor for the activation of reactants (*t*-BuOK/DMSO), preferably in two-fold excess, should be taken; the reagent should be capable of forming a carbanion stabilized by a high basic medium.

The electron transfer reactions attract ever-increasing attention.<sup>9–12</sup> The electron transfer from nucleophile to substrate is easily performed when the first has high energy HOMO, which corresponds to the first ionization potential, and the last has low energy, LUMO which corresponds to the reduction potential. Otherwise, the electron transfer is an extremely slow reaction.

Saveant and his team have used electrochemical methods to investigate the reactions, where nucleophiles themselves are weak electron donors (the case of a very slow electron transfer from reagent to substrate). Definition of standard potentials, RX/RX<sup>•-</sup> and Nu/Nu<sup>-</sup>, their internal barriers, and kinetic constants of cleavage of radical anions allowed the authors to show that the driving force of the reactions is

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the difference between the values of the standard potential and the peak potential on the cyclic volt–ampere curve. The decrease of the driving force leads to the change of the mechanism of the reaction from step to concert.<sup>13–15</sup> It is possible to expect experimental evidence of a single electron transfer in cases of very easily oxidizing nucleophiles and very easily reducing electrophiles. Therefore, from the point of view of a possible electron transfer, we are interested in the reactions where the probability of intermediate radicals formation is high enough, i.e. in the reactions of vicarious nucleophilic amination of nitroazoles.

There is only one example when the authors<sup>16</sup> have observed the formation of radical anions in VNS of hydrogen reaction of nitrobenzene with methyldichloroacetate, but the authors have neither described the method by which they registered radical anions nor have they presented their characteristics.

It is necessary to note that nobody except us investigated the VNS of hydrogen reactions by ESR. Therefore, we initiated the present investigation of VNS of hydrogen reactions of 1-methyl-4-nitropyrazole by ESR-monitoring in order to observe the possible free radical intermediates.

#### **RESULTS AND DISCUSSION**

In the preliminary communication,<sup>17</sup> it has been shown that the reaction of 1-methyl-4-nitropyrazole (1) with 1,1,1-trimethylhydrazinium iodide (2) in *t*-BuOK-DMSO leads to the formation of 5-amino-1-methyl-4-nitro-pyrazole (3) (Scheme 1):

The previous investigation of the mechanism of electrochemical reduction of nitroazoles has demonstrated that their *N*-alkylated derivatives form stable radical anions. But radical anions of *N*-unsubstituted nitroazoles are quickly decomposed, giving diamagnetic anions.<sup>18–20</sup> It has been observed that nitrogen-unsubstituted nitropyrazoles do not undergo amination under the conditions mentioned in the preceding text.<sup>17,21</sup>

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**Scheme 1.** The VNS of hydrogen reaction of 1-methyl-4-nitropyrazole (1) with 1,1,1-trimethylhydrazinium iodide (2).

It can be explained by the fact that the *NH*-bond in the nitroazoles dissociates in strongly basic media, and the value of reduction potential of the formed substrate anion is actually shifted toward negative field.

The supposition, given in the preceding text, is in agreement with the data on dinitropyrazole amination.<sup>22</sup> Obviously, the presence of two strong withdrawing groups in the molecule compensates the effect of the *NH*-bond dissociation. This conforms also to our earlier study of the electrochemical reduction mononitro- and dinitroderivatives of pyrazole and 1,2,4-triazole, which indicated that the first reduction potentials of dinitro derivatives are about 0.5 V more positive than that for their mononitro analogs.<sup>23</sup>

The use of 4-amino-1,2,4-triazole (4) as an amination agent results not only in 5-amino-1-methyl-4-nitropyrazole (3), but in another product identified as 1-methyl-4-nitropyrazol-5-yl(1,2,4-triazole-4-yl)amine (5) (Scheme 2).

In order to obtain the detailed information on the interaction of pyrazole nitro derivatives with amination agents **2** and **4**, the ESR-monitoring of the above reactions has been carried out. One should keep in mind that when the reactions are performed in an inert atmosphere (argon) the transitory intensive blue-violet coloring of the reaction mixtures, which rapidly turns to almost black, is observed. Earlier we had obtained the analogous results of studying VNS *C*-amination of 1-methyl-4-nitroimidazole.<sup>24</sup>

In the course of ESR-monitoring of the reaction mixtures of **1** with **2** or **4** in *t*-BuOK/DMSO, the well-resolved multiplets (*g*-factor 2.0034) are observed (Figs 1 and 2). They arise during 10-12 min after the beginning of the reaction and their intensities grow up to steady-state values.

The character and hyperfine structure (HFS) coupling constants obtained by the simulation provide evidence for the formation of primary radical anion **6** of 1-methyl-4-nitropyrazole (**1**) (Figs 1 and 2(b)). HFS coupling constants of radical anions **6** corresponds to the interaction of an unpaired electron with three nonequivalent nitrogen atoms, and with three equivalent and two nonequivalent protons, (mT): **3**(1N, NO<sub>2</sub>), **2**(1H, C-5), **2**(1H, C-3), **4**(3H, N-CH<sub>3</sub>), **3**(1N-2) and **3**(1N-1). Identification of the anion radical and assignments the HFS coupling constants were based on the ESR spectrum of 1-methyl-4-nitropyrazole radical anion (**6**) obtained independently by electrochemical reduction,<sup>19</sup>



**Scheme 2.** The VNS of hydrogen reaction of 1-methyl-4-nitropyrazole (1) with 4-amino-1,2,4-triazole (4).



**Figure 1.** The ESR spectrum recorded in the reaction of 1-methyl-4-nitropyrazole (1) with 1,1,1-trimethylhydrazinium iodide (2) in *t*-BuOK/DMSO under high resolution conditions: experimental spectrum, 30 min after the reaction start (a); simulated spectrum (b).



**Figure 2.** The ESR spectra recorded in the reaction of 1-methyl-4-nitropyrazole (1) with 4-amino-1,2,4-triazole (4) in *t*-BuOK/DMSO: modulation 0.125 mT (a); modulation 0.0125 mT (b).

by simulation and quantum-mechanical calculation of spin density distribution.



The experimental HFS coupling constants (mT) and quantum-mechanical calculated spin densities (in parentheses) are given in the formula **6**.

Possible ways of free radicals formation in the investigated reactions are given in Schemes 3 and 4. One could think that radical anions of the substrate are formed at the C–N-bond homolytical decomposition of  $\sigma^{\text{H}}$ -complex





**Figure 3.** The ESR spectrum recorded in the reaction of 1-methyl-4-nitropyrazole (1) with surplus of 1,1,1-trimethylhydrazinium iodide (2) in *t*-BuOK/DMSO (asterisks show the signals centers: \*g = 2.0044 corresponds to radical cation 9; \*\*g = 2.0034 corresponds to radical anion 6). Under low resolution conditions (a); under high resolution conditions (b); simulated spectra (c).



**Scheme 3.** Possible free radicals formation and their further reactions in the vicarious *C*-amination of 1-methyl-4-nitropyrazole by 1,1,1-trimethylhydrazinium iodide.

8, 11 (Schemes 3, 4), but quantum-mechanical calculation (B3LYP/6–31G\*) of geometrical parameters of  $\sigma^{\rm H}$ -complex 8 has demonstrated the lengthening of N–N-bond (1.489 Å) in its hydrazine fragment in the relation to N–N-bonds in (CH<sub>3</sub>)<sub>3</sub>N<sup>+</sup> N<sup>-</sup> H (7, 1.447 Å), as well as in the relation to hydrazine radical cations (9, 1.315–1.424 Å).<sup>25,26</sup> This means that N–N-bond must be the first to undergo the decomposition in the formed  $\sigma^{\rm H}$ -complexes, but not C–N-bond. Therefore, we think that the way of the radical anions formation due to  $\sigma^{\rm H}$ -complex decomposition is of low probability.

In agreement with this supposition is the fact that when 1-methyl-4-nitropyrazole (1) reacts with surplus 1,1,1-trimethylhydrazinium iodide (2) in *t*-BuOK/DMSO the ESR spectrum shows superposition of two signals with different *g*-factors: 2.0034 (corresponds to the radical anion substrate) and 2.0044 (Fig. 3).

The computer simulation of the last signal adequately reflects the experimental spectrum for the interaction of unpaired electron with two nonequivalent nitrogen atoms, one hydrogen atom, and with two groups of three and six hydrogen atoms having the following constants, (mT): **3** (1N, 0.790), **3** (1N, 0.170), **2** (1H, 0.200), **4** (3H, 0.100), **7** (6H, 0.073).

Unambiguous assignment of this signal presents some difficulties, although it is clear that the origin of this signal is connected with the aminated agent 1,1,1-trimethylhydrazinium iodide and was attributed to radical cation 9 (Scheme 3). The ground for such conclusion can serve well-known data on close structure (CH<sub>3</sub>)<sub>3</sub>N<sup>+</sup>-C<sup>•</sup>H<sub>2</sub>,<sup>26,27</sup> which is stable at ambient temperature in single crystals and has the same character of the hyperfine interaction and close values of HFS constants of methyl protons. The difference in values of HFS constants of NH-proton in radical cation (CH<sub>3</sub>)<sub>3</sub>N<sup>+</sup>-N<sup>•</sup>H in comparison with CH2-protons in radical cation (CH3)3N+-C•H2 may be explained by the influence of DMSO: including the sole molecule of dimsyl anion in calculation leads to decreasing of spin density on NH-proton from -0.0636 to -0.0082.

We consider that protons of methyl groups in radical cation  $(CH_3)_3N^+$ -N•H are not equivalent owing to the same reason as in radical cation  $(CH_3)_3N^+$ -C•H<sub>2</sub> – because of hindered internal rotation.<sup>26,27</sup> Quantum-mechanical calculations of radical cation 9 indicate that in every one of the three methyl groups two protons are almost equivalent and that sole has higher spin density (see formula 9 in the following text), which satisfactorily agrees with the experimental data.



**Scheme 4.** Possible free radicals formation and their further reactions in the vicarious *C*-amination of 1-methyl-4-nitropyrazole by 4-amino-1,2,4-triazole.

The analysis of the results allows to make an assumption that the direct electron transfer takes place from anion of reagent to substrate, which brings into existence the radical anions **6** (Schemes 3, 4). The absence of oxygen as well as the solvent properties (DMSO) prolongs the lifetime of radical anions and results in their accumulation in the solution.

The formation of product **5** can be explained by the addition of the neutral radical **10** to the initial substrate **1**, which gives the radicals **12**. The radicals **12**, as the result of their bimolecular interaction, lead to product **5** (Scheme 4). It is in agreement with the fact that the reactions of 1-methyl-4-nitropyrazole with 4-amino-1,2,4-triazole (**4**) in *t*-BuOK-DMSO in the ESR ampoules are always accompanied, as can be seen in Scheme 4, by the occurrence of molecular hydrogen, which is evolved as gas bubbles. Probably, the strong asymmetry of the ESR signal (Fig. 2a) can indicate the presence of radical **12** in the reaction mixture.

There is a need to note that products **3** and **5** cannot go through a common intermediate because in such a case the hydride anion must split off from  $\sigma$ -complex, which is impossible.



Further experiments will show whether observable radical anions of a substrate participate in the formation of  $\sigma^{\text{H}}$ -complexes or whether they are formed in a parallel proceeding reaction.

#### CONCLUSIONS

Thus, ESR-monitoring of the VNS C-amination reactions of 1-methyl-4-nitropyrazole allowed us to observe and identify primary radical anions of the substrate and to propose their possible formation mechanism. Obviously, radical anions of 1-methyl-4-nitropyrazole are formed as a result of direct electron transfer from anion of reactant, which is activated by the strongly basic medium *t*-BuOK/DMSO. It explains both the formation of the product **5** (Scheme 4), and the appearance of the signal in ESR spectra of the radical cation **9** while using the surplus **2** (Scheme 3).

#### **EXPERIMENTAL**

ESR Spectra were run on a SE/X-2547 spectrometer (Poland) in special cells in a dry argon atmosphere in carefully purified DMSO at room temperature for some hours. Oxygen was removed by blowing with dry argon. All reactants separately and in combinations of 2–3 components were checked in the absence of paramagnetism. When all the reactants in an inert atmosphere were mixed, a transitory blue coloring that rapidly changed to red–brown and then gradually to black was observed. The simulated spectra were obtained using the WINEPR SimFonia 1.25 Program (Bruker Inc. 1996). The quantum-mechanical calculations (HF/6–31G<sup>\*</sup>, B3LYP/6–31<sup>\*</sup>) were carried out using GAUSSIAN 98.<sup>28</sup>

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