

Formation of nitroxide radicals from secondary amines and peracids: A peroxy radical oxidation pathway derived from electron spin resonance detection and density functional theory calculation

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Abstract

By electron spin resonance (ESR) detection and quantum chemical calculation based on the density functional theory (DFT) at the B3LYP/6-31G(d) level, we found that the formation of nitroxide radicals from secondary amines and peracids is a peroxy radical oxidation reaction, where peroxy radicals are the reactive intermediates of peracids in the oxidation. The DFT calculation revealed the transition structures and activation barriers of oxidizing pyrrolidine by the peroxy radicals of peracetic acid and percarboximidic acid. Their barriers are 11.75 and 12.35 kcal/mol, respectively, showing that the peroxy radicals have high reactivity on secondary amines. A reaction path calculation (IRC) of the oxidation of pyrrolidine by the peroxy radical of percarboximidic acid illustrated the process of the formation of nitroxide radical: firstly, the terminal oxygen atom of the peroxy radical R–O–O• attacks the nitrogen atom of secondary amine and forms a N–O bond, and then the hydrogen atom from the N–H of the secondary amine is transferred to the imido nitrogen atom or the carbonyl oxygen atom of peracid and finally forms a new N–H or O–H bond.

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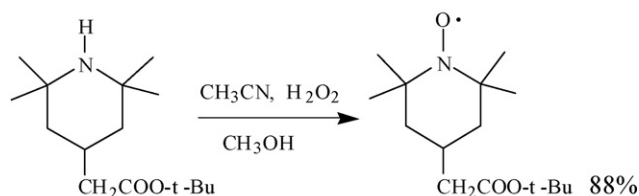
Keywords: Secondary amine; Peroxy radical; Nitroxide radical; ESR detection; DFT calculation

1. Introduction

Stable nitroxide radicals as spin labels and spin probes play important roles in the study of biological systems using electron spin resonance (ESR) spectroscopy. Since the 1960s, a large number of experimental and theoretical research projects have been carried out to investigate the synthesis, structure, properties and application of nitroxides [1–21]. Preparation of nitroxide radicals through oxidization of secondary amines by peracids has been the most important synthesis method and has been extensively investigated. Among peracids, *m*-chloroperbenzoic acid (MCPBA) is the most effective and most widely used oxidant [8–18]. Peracetic acid is also used sometimes [19–21].

The acetonitrile-hydrogen peroxide method of Payne et al. [22] is another useful procedure for preparing nitroxide radicals. For example, the ester secondary amine was oxidized at room temperature to a nitroxide radical with a yield of 88% as shown

below [23]. However, this actually can also be ascribed to the method of using peracids because in the reaction the acetonitrile would first be changed into percarboximidic acid as mentioned later.



Throughout the last 40 years, although many nitroxide radicals have been synthesized, the mechanism of their formation remains unclear. To date, it is still not understood how secondary amines change into nitroxide radicals. The questions are what the reactive intermediate of the reaction is, what the transition structure is, how high the activation barrier of the oxidation reaction is, how the unpaired electron of nitroxide is produced and how the relative atoms are transferred.

By a quantum chemical calculation with the density functional theory (DFT) at the B3LYP/6-31G(d) level, it was found

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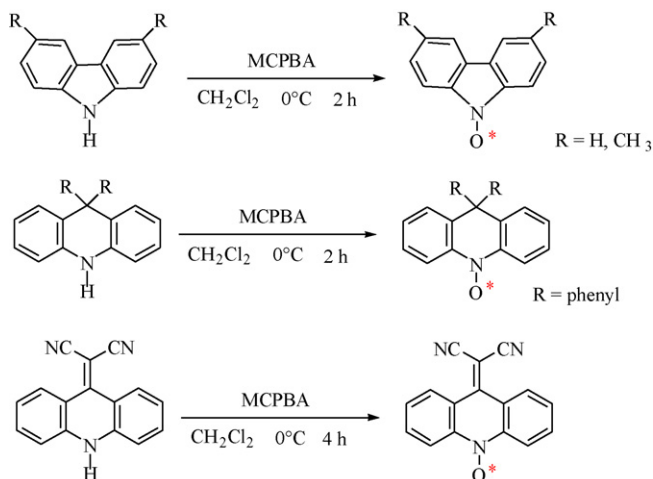
that the formation of the nitroxide radicals is a radical oxidation reaction of secondary amines by peroxy radicals. The peroxy radicals are the products from peracid molecules missing the H atoms in the $-OOH$ groups. The transition structures (TS) and the activation barriers of oxidizing pyrrolidine by the peroxy radicals $CH_3C(O)OO^\bullet$ and $CH_3C(NH)OO^\bullet$ were obtained. The barriers were low; only ~ 10 kcal/mol. ESR detection also indicated that the activation barriers in the formation of nitroxide radicals are fairly low. A reaction path calculation (IRC) revealed the microscopic process of forming nitroxide radicals.

2. Experimental

All the chemical reagents were commercial guaranteed reagents, and were used without any further purification. The samples used for ESR measurements were prepared by adding pyrrolidine or dimethylamine and 30% of H_2O_2 into CH_3CN-H_2O (v/v, 20:80). The concentration of pyrrolidine or dimethylamine was about 0.3 M, and the concentration of H_2O_2 was about 1.0 M. The pH values of the solution were 9.0–10.0 because the secondary amines were basic. In the preparation, it was observed that some O_2 bubbles were released. All ESR spectra were recorded at room temperature using a Bruker ER-200D spectrometer.

3. Quantum chemical calculations

The DFT calculation was carried out with the Gaussian 98 program package [24]. In the last decade, the DFT method has become an important tool in clarifying reaction mechanism, especially for some difficult controversial mechanistic problems [25–31]. Recently, Schiemann and co-workers [8] used the DFT method to calculate the electric structures of some aromatic nitroxide radicals, obtaining result that is in very good agreement with the experimental data. Therefore, in the present study we selected the DFT method to explore the mechanism of the formation of nitroxide radicals from secondary amines and peracids. Geometry optimizations of radical or non-radical



Scheme 1. The nitroxide radicals generated at $0^\circ C$.

Table 1
ESR spectral parameters of the radicals **5** and **3**

Radical	g_{iso}	$a(N)$ (mT)	No. of nitrogen	$a(H_\beta)$ (mT)	No. of proton
I	2.0069	1.51	1	1.96	4
II	2.0060	1.59	1	1.08	4

molecules, the geometries of transition structures, potential energy surface scans (PES), reaction path calculation (IRC), and estimation of solvent effects by using the polarizable continuum model (PCM) (32–35) were all carried out at the B3LYP/6-31G(d) level. Obviously, using the same calculation method, level and basis set is favorable for comparing the data and achieving reliable conclusion.

4. Results and discussion

4.1. Formation of nitroxide radicals is a reaction process with low activity barriers

The oxidation of secondary amines by peracids often occurs at temperature between 0 and $25^\circ C$. Recently, Schiemann and

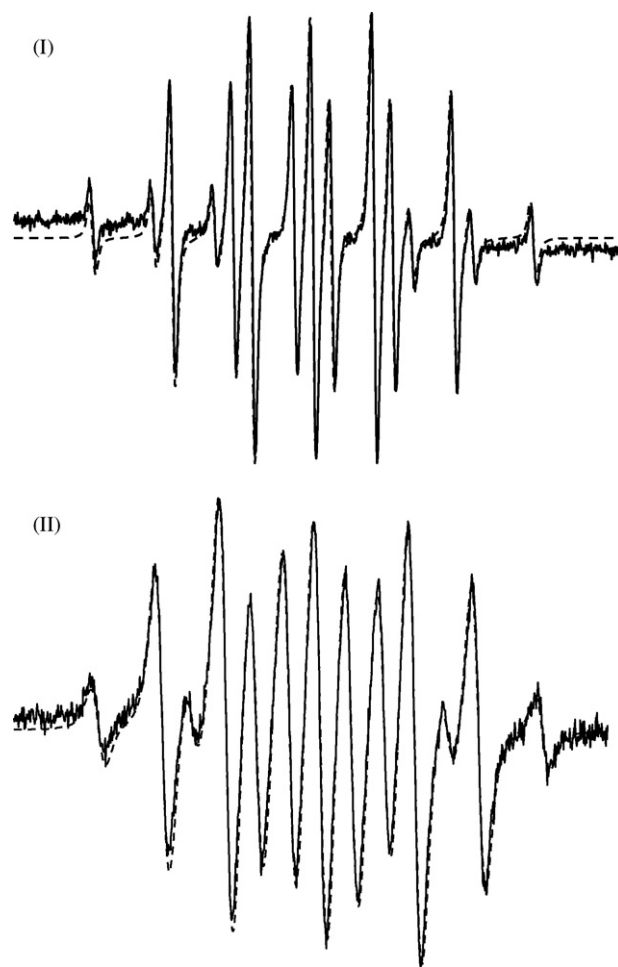


Fig. 1. Experimental (solid line) and computer simulated (dashed line) ESR spectra of pyrrolidine-N-oxide radical (I) and dimethylamine-N-oxide radical (II) at room temperature.

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