Predictive capacity of semi-empirical MNDO/PM3 and molecular mechanics MM2 estimations of the reactivity of cyclic nitrones as spin traps

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Abstract

It is shown that the reactivity of nitrone compounds in spin trapping reactions (addition of short-lived free radicals to the nitrone double bond) can be predicted by means of not very complicated semi-empirical procedures simulating a hypothetical adsorption complex and its further transformation into spin adducts. Thus estimated reaction characteristics (the site of radical addition to a nitrone, stability of the resulting spin adduct, the effect of its geometry on hyperfine splitting constants in the EPR spectra of spin adducts) generally agree with the experimental data available on these nitrones.
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1. Introduction

The application of organic compounds as receptors for reactive species, both in the gas phase and in liquid, is under intense investigation at present. For instance, the authors of [1] proposed a sensor based on an organic polymer containing amine group with different substituents. Various examples of the use of phthalocyanines and porphyrins as sensors for Cl_2, NO_2, and NO were described in [2–6]. In order to search for a suitable receptor, we carried out simulation of the adsorption complex [7]. In the present work, nitrone compounds are investigated as receptors by means of semi-empirical simulation. The results of previous simulation revealed that an adsorption complex (AC) between a reactive species and a nitrone is always formed at the carbon atom of the nitrone group, whatever species adds. The structure of the AC can be investigated by means of IR spectroscopy [8]. An interesting possibility to carry out experimental verification of the position at which the addition proceeds is provided by the spin trapping procedure. The addition of a short-lived free radical to a nitrone molecule – spin trap (ST) – results in the formation of a spin adduct (SA) which is a long-lived (stable) nitroxide radical. Its formation is easily detected as the appearance of an EPR spectrum with the hyperfine splitting at the nitrogen atom of the nitrone group (and additional splitting at H atoms, if there are any in the beta-position to the radical centre formed) [9].

Free radicals play an important part in chemical and biological processes [9]. Spin trapping is one of the tools to investigate these species. Nitrone compounds have been proposed as ST for this purpose. Trapping a radical they form a spin adduct which is a nitroxide radical. The latter compounds are widely used as spin labels and paramagnetic probes to investigate molecular dynamics and structure of liquids, polymers and biological systems. In addition, nitroxide radicals are convenient systems for testing the applicability of various approximations in quantum chemical simulations of molecular systems and in theoretical estimations of the potential reactivity. The reactivity of nitrones toward free radicals strongly depends on the functional groups and substituents present in a nitrone molecule. The data available from the literature [10] allow

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assuming that introducing various substituents one may achieve selectivity of ST to the kinds of free radicals, which will broaden the possibilities of spin trapping procedure for identification of reactive short-lived intermediates in multi-stage processes.

It is shown in the present work that not very complicated semi-empirical (MNDO/PM3) and molecular mechanics (MM2) simulation of the structure of an adsorption complex, formed when a short-lived free radical approaches the nitrone molecule and gets adsorbed at a definite site of it, and simulation of the structure of nitrone spin adducts may provide satisfactory explanations of some regularities observed experimentally; simulation results also allow one to avoid unnecessary synthesis efforts and to choose the structures of desired compounds for specific tasks when identifying reaction mechanisms in a broad range of systems.

In order to illustrate the developed approach, we simulated the reactivity of nitrones toward the hydroxyl radical OH. The results of simulation were compared with the available experimental observations of nitrone behaviour toward short-lived free radicals [11–13]. We also made some additional (lacking) experiments to test the results obtained by simulation.

2. Experimental

The EPR spectra of some spin adducts were recorded with a Bruker ER-200 D-SRC spectrometer in a standard quartz cell. The stability of magnetic field was 2 mT/h. Microwave power was not higher than 10 mW, modulation amplitude was 0.03–0.10 mT. Microwave frequency was 100 kHz, receiver gain 1×10^4–6.32×10^5. Time constant was 0.2 s, scan rate was 10 mT/200 s. Instrumental error of measuring the constants of hyperfine splitting was 0.004 mT. Short-lived free radicals were generated by UV irradiation of aqueous solutions of H_2O_2 (to produce ·OH), with methanol or ethanol added (to produce ·CH_2OH or ·CH_2CH_2OH, respectively), using the same generation procedure as that described in [11–13].

3. Modeling and verification

The semi-empirical methods can be optimized for different purposes. For instance, MNDO, AM1, and PM3 methods were designed to reproduce heats of formation and structures of a large number of organic molecules. PM3 is much better than AM1 in calculating heats of formation for nitrogen-, sulphur- or phosphorus-containing organics (the accuracy is 4–5 times better in comparison with AM1). DM3 is used to calculate spin densities (for radical structures).

We consider a model situation which consists in physical adsorption of a short-lived free radical (OH) on a nitrone molecule; physical adsorption involves only weak interactions since it is caused not by electronic transitions but only by some changes in electron motion in the adsorbate and

adsorbent molecules. The adsorbed particles conserve their nature; they remain unchanged in the chemical sense. Thus, when considering this hypothetical state which we call adsorption complex (AC), we calculate small changes in energy levels of the nitrone molecule induced by the approaching short-lived free radical. Finally, we compare the energies of the initial unperturbed nitrone molecule, of the adsorption complex, and of the product of radical addition (spin adduct). Comparing relative positions of these three levels we evaluate the possibility of the addition to proceed.

In order to achieve this goal, we carried out a full calculation of the interaction of OH with nitrones using quantum-chemical semi-empirical methods (MNDI, AM1, and PM3) and molecular mechanics (MM2).

We searched for the minimum of the total energy as a function of atomic coordinates. The procedure in general allows obtaining the data on molecular geometry, dipole moment, heat of formation [14].

The structure of each nitrone and the corresponding adsorption complex was optimized using MNDO, AM1, and PM3. The MNDO- and AM1-optimized structures were each optimized using MM2, to calculate the structure of adsorption complexes. The calculation algorithm was the same at that described in [14,15]; CS Chem 3D Pro software (Cambridge Soft Corporation, USA) was used.

Simulation was carried out in several steps:

(1) Search for a centre at which a radical is adsorbed. Physical adsorption of a radical approaching a nitrone molecule is considered; the formation of a structure with reasonably short distance between the radical and the nitrone, corresponding to the minimal energy, is a criterion of the occurrence of adsorption (the formation of adsorption complex): MNDO/PM3.
(2) Determination of the structure of this adsorption complex (bond lengths, valence angles): PM3 + MM2.
(3) Determination of the structure of reaction products – spin adducts: MM2.

The compounds containing one or two nitrone groups were considered. Their structures are shown in Fig. 1. For convenience of consideration, some atoms are numbered.

4. Results and discussion

Compound **I**: 1,2,2,5,5-pentamethyl-3-imidazoline-3-oxide (PMIO) [11,13]. A specific feature of its structure is the presence of the amine nitrogen atom which can be protonated. It was reported that the hyperfine splitting constants (hfc) of protonated and non-protonated spin adducts of the same radical differ substantially: for non-protonated adduct of OH, $a_N = 1.46$ mT, $a_H = 1.72$ mT; for the protonated one, 1.38 and 0.45 mT, respectively.

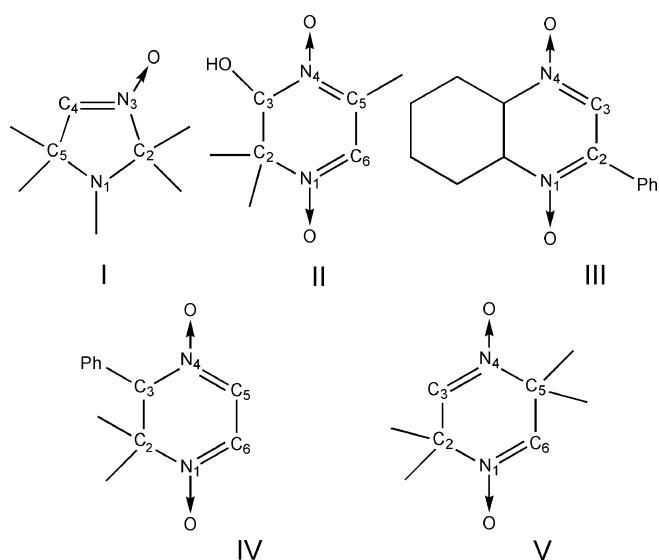Fig. 1. The structures of nitrones involved in the present study.

Table 1
Some distances between atoms in nitrone I and its spin adduct (non-protonated and protonated)

Bond length (distance)	ST (Å)	(ST–H)$^+$ (Å)	SA (Å)	(SA–H)$^+$ (Å)
C4–N3	1.417/1.36	1.823/1.07	1.419/1.36	1.451
C4–C5	1.503	1.496	1.533	1.537
N1–C5	1.470	1.523	1.457	1.533
N1–C2	1.476	1.531	1.464	1.506
C2–N3	1.520	1.597	1.465	1.438
N3 → O	1.324	1.358	1.325	1.316
O···H	2.807	2.890	2.448	2.415

Note: Slashes indicate the calculated bond order.

One can see that the hfc at the hydrogen atom changes most substantially (by a factor of 3) [11]. Spin trapping and protonation reactions are shown together schematically in Fig. 2.

Calculation of the structure of the OH-PMIO spin adduct shows that protonation causes substantial changes in the molecular geometry. Some important distances in the protonated and non-protonated forms of ST and SA are shown in Table 1. Protonation causes an increase in the C4–N3 distance by approximately 0.4 Å; this distance is directly connected with the density of the unpaired electron in the point of the nucleus of β-hydrogen atom. Another reason is protonation-related distortion of planarity. This causes a decrease in the density of s-electron 'cloud' at the indicated H-atom nucleus point.

Compound **II**: 3-hydroxy-2,2,5-trimethyl-2,3-dihydro-pyrazine-1,4-dioxide (HDPDO) [12,13] has two conjugated
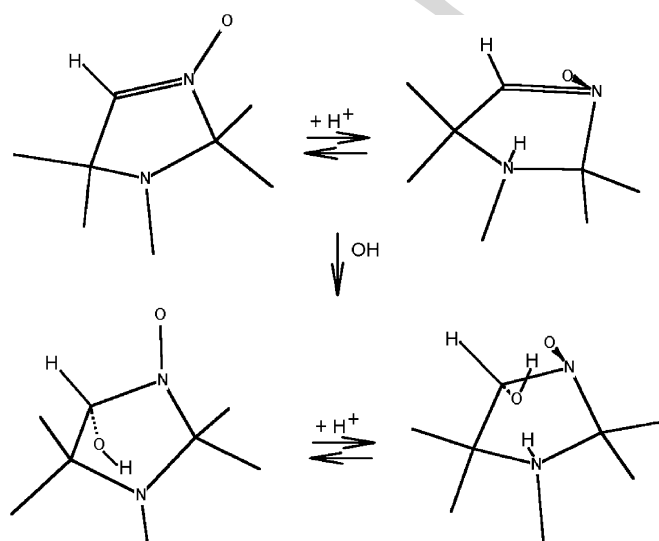

Fig. 2. Protonation of the imidazoline spin trap **I**.

nitrone groups. They differ from each other in the number of H atoms in β-position (with respect to the radical centre formed when OH is trapped). This difference allows one to determine the position of radical addition on the basis of the number of lines in the EPR spectrum of the spin adduct.

There are two possible positions for OH addition to HDPDO molecule: 5 and 6. Simulation of the structures of the corresponding two kinds of spin adducts shows that the addition of OH at position 5 (CH$_3$) results in two possible SA configurations differing from each other in energy by 17 kcal/mol; if the energy level of the most profitable configuration of spin adduct formed at position 5 is taken as zero, the addition at position 6 corresponds to the energy of 13 kcal/mol. Therefore, OH addition can proceed only at position 5. Consideration of the formation of AC for this reaction shows that the most favourable position for OH addition is position 5.

Experiments showed that the addition of short-lived free radicals to dinitrone **II** results in the formation of spin adduct with only one radical centre (no biradicals were detected); another experimentally established fact is that the EPR spectrum of the OH-HDPDO spin adduct is a triplet of doublets (six lines); this means that OH adds only to position 5. So, theoretical consideration is in good agreement with the experimental observation of the position of OH addition to compound **II**.

Compound **III**: hexahydroquinoxaline-1,4-dioxide with phenyl substituent in position 2 is another conjugated dinitrone differing form compound **II** by the presence of phenyl group (in position 2) and a cycloalkyl fragment. These differences in structure bring about sharp differences in the reactivity: compound **III** does not form any adducts with OH; however, it was observed to trap hydroxyethyl radical C$_2$H$_4$IH. Let us consider the addition of short-lived free radicals through the formation of an AC. Simulation shows that compound **III** forms an AC with radicals at position 3. The calculated energy diagrams of the reactions for the three kinds of radicals are shown in Fig. 3. Though the formation of an AC with OH is profitable from the viewpoint of energy (see Fig. 3), about 30 kcal/mol is necessary for the final product to be formed (by OH addition to position 3); this means that the addition of OH does not give any energy gain; the probability of this reaction is very low. So, adduct with OH at position 3 is not formed.
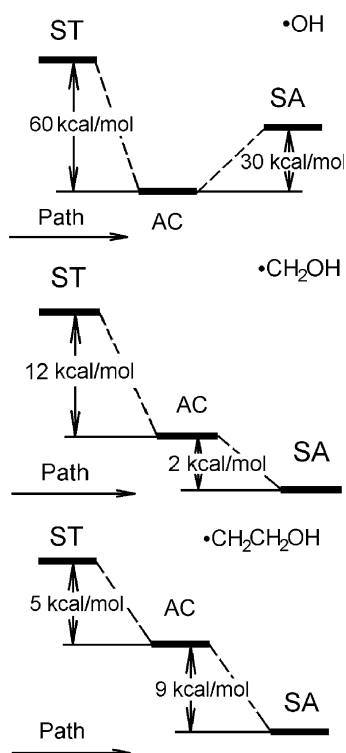
Fig. 3. Energy diagrams for dinitrone **III** forming SA through the adsorption complex (AC) with free radicals: ˙OH, ˙CH₂OH, and ˙CH₂CH₂OH.

Fig. 4. Examples of EPR spectra of the spin adducts of dinitrone **III** with different radicals.

In the case of hydroxymethyl radical (see Fig. 3), energy is released with the formation of AC (∼12 kcal/mol); further, with the addition of the radical, ∼2 kcal/mol is released. A similar situation is observed for hydroxyethyl radical (see Fig. 3), but energy gain in the formation of the spin adduct is 9 kcal/mol. So, it may be stated that addition at position 3 is most profitable for the hydroxyethyl radical. The addition of hydroxymethyl radical is also possible at this position, but the concentration of the formed spin adduct should be lower. We verified this theoretical result in a special experiment involving trapping of OH, CH₂OH and C₂H₄OH radicals with compound **III**. The result is shown in Fig. 4. The structure of these EPR spectra proves that the radicals add at position 3 of nitrone **III**. The spectrum of the adduct of hydroxyethyl radical is more intensive than that of hydroxymethyl. This confirms our theoretical result that the concentration of CH₂OH adduct should be lower. No adduct is observed with OH, exactly as predicted by simulaiton. In this case, too, we observe a good agreement between theory and experiment, which confirms our model of SA formation through an AC.

Compound **IV**: 2,2-dimethyl-3-phenyl-2,3-dihydropyrazine-1,4-dioxide traps OH with the formation of a spin adduct. The EPR spectrum of the adduct contains 12 lines. The number and shapes of lines suggest that OH adds at position 5 (otherwise the spectrum would contain only a triplet of doublets, 6 lines, because there is only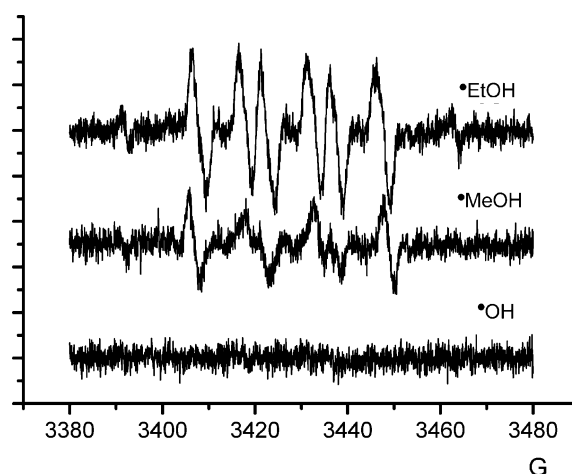 one β-hydrogen atom if the radical adds at position 3) (see Fig. 1 **IV**). Simulation was performed for this compound; it was shown that **IV** forms an adduct with OH. Position 5 is preferable, both for the formation of an AC and for the formation of the final product of radical addition. Addition to a different position is by 14 kcal/mol less profitable. So, theoretical consideration suggests that radical addition proceeds at position 5.

Compound **V**: 2,2,5,5-tetramethyl-2,5-dihidropyrazine 1,4-dioxide (5) (DPDO) is a six-membered heterocycle with isolated double bonds [13]. The molecule is symmetrical, so the two nitrone groups are fully equivalent. It is known from experiments that this compound acts as a spin trap forming adducts with only one radical centre. Biradicals never were observed.

Simulation gives exactly the same result. Calculation confirms that **V** forms an AC with one OH radical. As soon as one radical has been trapped, the adduct with the second radical cannot be formed, since the addition of the second OH is unfavourable from the viewpoint of energy.

5. Conclusions

On the basis of results obtained in semi-empirical simulation of the adsorption complexes and the resulting spin adducts, one may predict the structure of SA, and the reactivity of nitrones as spin traps. In the case of asymmetrical nitrones, calculation helps predicting the position of radical addition; in the case when amine nitrogen atom is present in the molecule (imidazoline derivative), protonation-caused changes in the geometry of the nitrone and its spin adduct can be revealed. This is confirmed experimentally by the EPR spectra of spin adducts which change with changes in the acidity of solution. It is shown that the energy diagrams depicting the formation of an adsorption complex between a short-lived free radical and a nitrone molecule help predicting the stability of spin adducts. So, semi-empirical calculations can be used to predict the reactivity of nitrones as spin traps thus saving synthetic effort

and simplifying experimental search for compounds to trap and identify short-lived free radicals of different kinds.

Acknowledgements

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