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Spectrochimica Acta Part A 69 (2008) 1367–1371

SPECTROCHIMICA ACTA PART A

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Studies on electron spin resonance spectroscopy of biradical molecules containing ^{14}N-O and ^{15}N-O moieties

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Received 6 August 2007; accepted 17 September 2007

Abstract

The biradicals with ^{14}N-Oxide and ^{15}N-Oxide at the both ends of a molecule are synthesized for the molecular ruler of protein structure, and a potential device for quantum computing. We also establish a general synthetic method for reliable biradical formation. ESR spectra are recorded for the biradicals containing ^{15}N-Oxide and ^{14}N-Oxide with various interdistance separations. We find that two types of biradicals yielded different ESR spectra depending upon the distance between the ^{15}N-O and ^{14}N-O moieties in a molecule. This is due to electron spin dipole–dipole interaction occurring between the radicals. We also find that there is an indication of isotopic nuclear effects in the dipole–dipole interactions. The present study implies feasibility of the distance measurement between two different N-Oxides containing ^{14}N and ^{15}N isotopes. We conclude that quantum entanglement effects are observed through the dipolar interactions, which enable application of quantum computing devices operating in the liquid state.

Keywords: Biradical; Electron spin resonance; N-Oxide; Aromatic dicarboxylic acid type radical; Urea type radical

1. Introduction

Biradical compounds have two unpaired electrons in the same molecule. Various biradical compounds containing N-Oxides have been reported [1–3]. Biradicals are employed as spin label agents in the life science, oxidizing agents in the organic chemistry and organic magnetic materials in physics [4]. There is an existing method of synthesizing two ^{14}N-Oxides simultaneously, attached to an ester which provides the basic frame parts. On the other hand, biradicals of ring structure, like the adamantane types are generated by synthesizing two basic frames with an N-Oxide each [5–7].

The present study aims at the synthesis of biradical compounds applicable to life science and quantum computing. In quantum computers, it is necessary to make input and output terminals independent and to discriminate between them. Therefore, the target biradical compound has ^{14}N-Oxide and ^{15}N-Oxide moieties in the same molecule. In life science, however, compounds where the distance between the ^{14}N-Oxide and ^{15}N-Oxide moieties differ are needed for distance information measurement of biomolecules [1]. Hence, we aimed to establish a simple synthetic method which can vary the distance and the direction between radicals in a biradical compound.

In order to fulfill these purposes, known biradicals have three problems. (1) Both N-Oxides in the same molecule are ^{14}N (natural abundance 99.6%). An adamantine type compound cannot be used to synthesize other compounds where the distance and direction can be changed by the same synthetic method [4–7]. (2) A straight chain can change the distance between N-Oxides by the existing synthetic method [1]. However, in a straight chain the distance cannot be determined, as a result of the rotational isomers of the carbon chains. (3) Transesterification occurs in ester bond. From these problems, a biradical compound fulfilling two conditions is considered as the fundamental indicator of a synthetic method. One of the conditions is that the biradical compound should have a ^{14}N-Oxide and ^{15}N-Oxide in the same molecule. Another condition is to have a biradical where the distance between the N-Oxides can vary.

The reason for using amide bonds is that the target biradical compounds have a ^{14}N-Oxide and ^{15}N-Oxide in the same molecule. ^{14}N and ^{15}N are core isotopes. If transesterification happens, a biradical compound containing a ^{14}N-Oxide and ^{14}N-

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doi:10.1016/j.saa.2007.09.037

Oxide, or ^{15}N-Oxide and ^{15}N-Oxide can be resulted by the reaction. On the other hand, we considered a combination of a basic frame and an amine, using an amide bond. Amide bonds are the molecular structures that are used for proteins or peptides. Since they are more stable than ester bonds, transesterification does not occur. Reaction conditions including a strong acid or strong base are required for cleavage of an amide bond. So, they do not cleave under ESR measurement conditions. When introduced into biomolecules, the cleavage and joint position does not change simply, either. It is necessary to use an amine which can be purchased containing both ^{14}N and ^{15}N for the amide bonds. Therefore, 1-^{14}N-4-amino-2,2,6,6-tetramethylpiperidine and 1-^{15}N-4-amino-2,2,6,6-tetramethylpiperidine were used as moieties containing a nitroxide. Furthermore, the technique to form peptide bonds was used. Dicyclohexylcarbodiimide (DCC) and 1-hydroxy-1H-benzotriazole (HOBt) are peptide bond condensing agents that have been used for many years. 4-(4,6-Dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMT-MM) is a new condensing agent which can be used in polar solvents like alcohol [8–12]. A synthetic process was examined using many condensing agents besides these (Fig. 1).

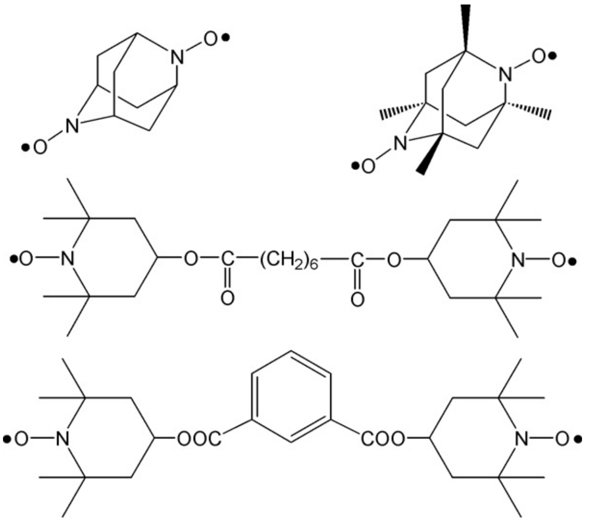


Fig. 1. Various type of biradical compounds thus far reported.

The reason for using an aromatic dicarboxylic acid for the frame portion: In the present study, variable distance and direction between the ^{14}N-Oxide and ^{15}N-Oxide moieties is the aim for the generation of various biradical compounds. Therefore, an aromatic dicarboxylic acid was used for the basic frame portion. As a result, the distance and direction between the biradical moieties can be changed by changing the joint position of the two carboxylic acid groups on the basic frame, while using the same synthetic method. Varying the central number of aromatic rings can also make the distance between nitroxide variables (Fig. 2).

In the present study, we aim at a general synthetic method for biradical compounds that have a ^{14}N-Oxide and ^{15}N-Oxide at both ends of a molecule from 4-amino-2,2,6,6-tetramethylpiperidine and an aromatic dicarboxylic acid. Furthermore, we defined ESR parameters such as D and J terms for the distant measurement as well as the spin exchange rate (Fig. 3).

2. Experimental

2.1. Synthesis

The chlorine of **1** was first replaced with amine **5** to give **2** in 36% yield. Replacement of the PhO group of **2** with amine 5-**^{15}N** afforded urea **3** in 66% yield. Biradical **4** was obtained by oxidation with *m*-chloroperbenzoic acid in 95% yield (Fig. 4).

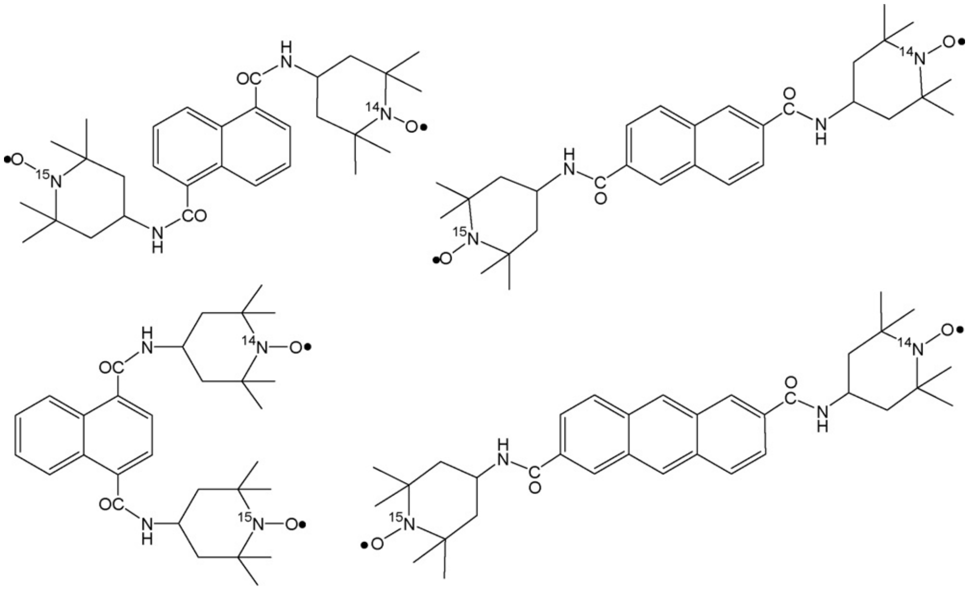


Fig. 2. The biradical compounds with aromatic carboxylic acid.

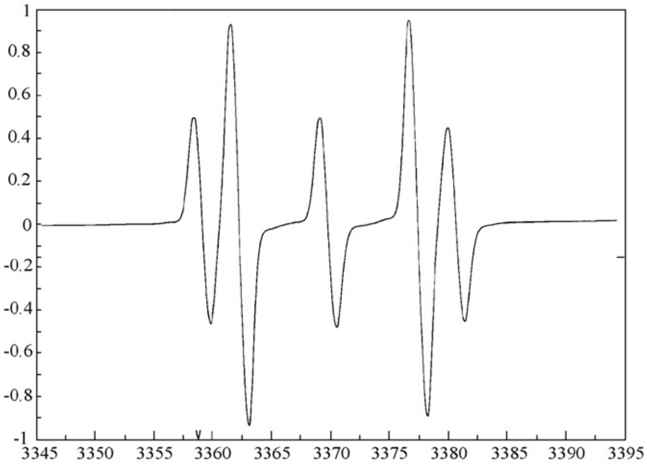


Fig. 3. An ESR spectrum of aromatic diamide-type compound with ^{14}N- and ^{15}N-Oxides.

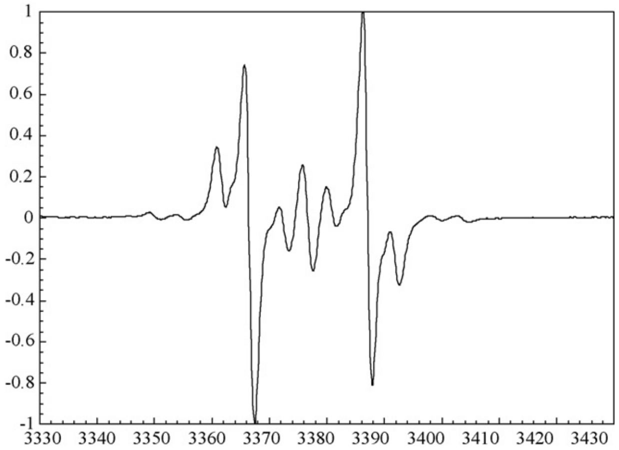


Fig. 4. An ESR spectrum of urea-type compound with ^{14}N- and ^{15}N-Oxides.

Synthesis of biradical **9** having the aromatic diamide moiety was as follows. Half-ester **6** and amine **5** ware coupled with DMT-MM to give monoamide **7** in 63% yield. Hydrogenation of **7** with Pd-C afforded the carboxylic acid in 33% yield. Condensation of the carboxylic acid and amine **5-^{15}N** with DMT-MM afforded the diamide **8** in 87% yield. Finally biradical **9** was obtained by oxidation of **9** with *m*-chloroperbenzoic acid in 73% yield.

2.2. ESR spectroscopy

ESR measurements were carried out using an ESR spectrometer (JEOL, JES-FEIXG). All the ESR spectra were recorded at the X-band (9.3 GHz). The microwave field strength was varied from 0 to 64 mW. Magnetic field modulation was operated at 100 kHz. The solvent in the present study is dichloromethane for the all the ESR measurements. All the measurements were made at room temperature (approximately 20 °C).

3. Results

3.1. Synthesis

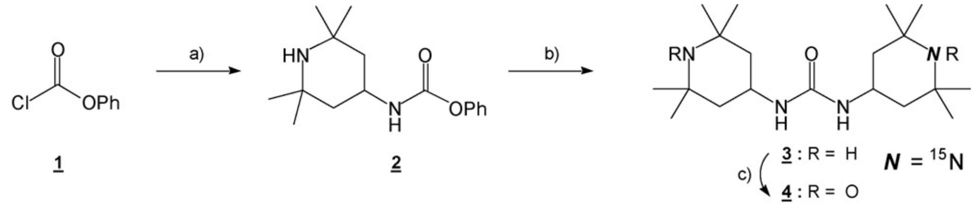
We established a general synthetic method for biradical compounds containing a ^{14}N-Oxide and ^{15}N-Oxide in the same molecule.

The synthetic method for urea type molecules is as follows. The chlorine of chloride **1** was first replaced with 4-amino-2,2,6,6-tetramethylpiperidine-^{14}N **5** to give the amide compound **2** in 36% yield. Replacement of the PhO group of the generated compound **2** with 4-amino-2,2,6,6-tetramethylpiperidine-^{15}N **5-^{15}N** afforded urea compound **3** in 66% yield. Biradical compound **4** was then obtained by oxidation with *m*-chloroperbenzoic acid in 95% yield (Scheme 1).

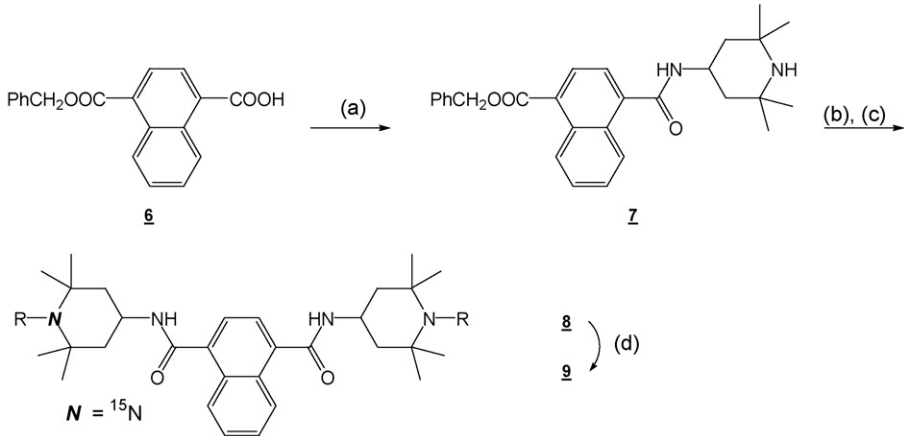
The general synthetic method for aromatic diamides was studied using 1,4-dicarboxylic acid. Half-ester **6** and amine **5** were coupled with DMT-MM to give monoamide **7** in 63% yield. Hydrogenation of **7** with Pd-C afforded the carboxylic acid in 33% yield. Condensation of the carboxylic acid and amine **5-^{15}N** with DMT-MM afforded the diamide **8** in 87% yield. Finally, biradical compound **9** was obtained by oxidation of diamide **8** with *m*-chloroperbenzoic acid in 73% yield (Scheme 2).

3.2. ESR spectral analysis

ESR spectral measurements were carried out on the urea type and the aromatic diamide type biradicals generated by the synthetic procedures described above. The analysis of the ESR spectra revealed the magnetic interaction parameters of the two biradical molecules (Table 1). In the urea type, the nuclear coupling constant *a* was as follows. It was $a = 1.41$ mT in the ^{14}N-Oxide, and $a = 1.93$ mT in the ^{15}N-Oxide. The exchange interaction was $J = 13.6$ (MHz). The *D*-term of ^{14}N-Oxide and ^{15}N-Oxide were found to be 30.6 and 10.8 MHz for urea and diamide types, respectively. These values remain constant irrespective of ^{14}N-Oxide and ^{15}N-Oxide moieties. This is due to the distance dependency of the *D*-term. By comparing the obtained *a* and *J*, it became apparent that $J < a$. From this result, and since only a short distance exists between the two N-Oxides, the urea type biradical compound has a strong dipole



Scheme 1. Preparation of urea derivative **4**. (a) 4-amino-2,2,6,6-tetramethylpiperidine **5**, NaOH, H_2O, Et_2O, 36%; (b) 4-amino-2,2,6,6-tetramethylpiperidine-^{15}N **5-^{15}N**, NaOH, H_2O, THF, 66%; (c) *m*-chloroperbenzoic acid, 95%.



Scheme 2. Preparation of 1,4-dicarboxylic acid diamide **9**. (a) 4-amino-2,2,6,6-tetramethylpiperidine **5**, DMT-MM, CH_3OH, 63%; (b) H_2, Pd-C, EtOH, 33%; (c) 4-amino-2,2,6,6-tetramethylpiperidine-^{15}N **5-^{15}N**, DMT-MM, CH_3OH, 87%; (d) *m*-chloroperbenzoic acid, 73%.

Table 1
Parameters of magnetic interaction for various nitroxide compounds

Nitroxide compounds	*a* (mT)	*g*-value	*D* (MHz)	*J* (MHz)
Urea				
^{14}N-Oxide	1.41	2.002	30.0	13.6
^{15}N-Oxide	1.93	2.001		
Arometic diamide				
^{14}N-Oxide	1.44	2.005	10.8	0
^{15}N-Oxide	2.03	2.005		

interaction. In the aromatic diamide, was $a = 1.44$ mT in the ^{14}N-Oxide, and $a = 2.03$ mT in the ^{15}N-Oxide. *J* was $J = 0$ MHz. From these results, since there is a long distance between the two N-Oxides, the aromatic diamide biradical compound is in a state in which a dipole interaction can almost be disregarded. In case of short distance between the two N-Oxides, the dipole interaction becomes stronger. However, it turns out that this can be mostly disregarded over a longer distance. It is possible to measure the distance between the ^{14}N-Oxide and ^{15}N-Oxide from the difference in the exchange interaction in the ESR spectrum. Therefore, we find that the distance between two spin labels in a molecule is able to be measured from the ESR spectrum.

4. Discussion

4.1. Synthesis of biradicals

The present study has two outstanding points as compared with the composition of biradical compounds which have thus far been reported. An aromatic dicarboxylic acid was used as the substrate in this research. This molecule has two carbonyl groups on an aromatic ring. It is possible that the composition of biradical compounds in which the direction and distance between the N-Oxide moieties differ can be synthesized by using a substrate in which the joint positions of the carbonyl groups differ. In this research, the central compounding method for biradical compounds having both a ^{14}N-Oxide and ^{15}N-Oxide in the same molecule was established. By using this compounding method, aromatic diamide type biradical compounds which have different directions and distances between the N-Oxide moieties can be synthesized easily by the same compounding method. 4-(4,6-Dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMT-MM), which is a new condensing agent developed in recent years, has three outstanding points as compared with other condensing agents [4–8]. (1) Polar solvents, such as alcohol, can be used. (2) It is not hygroscopic and is stable. (3) Reaction operation is very easy. The one-step operation of adding DMT-MM, an amine and a substrate which has a carbonyl group can generate an amide combination. There are condensing agents such as DCC and HOBt which have been known for many years. DCC and HOBt require complicated synthetic operations and after-treatment compared with DMT-MM. The execution of the condensation reaction became easy compared with former procedures, because using DMT-MM raises the solubility of substrate, and is easily handled.

4.2. Physical interaction in biradical

The hyperfine coupling constant of the ^{14}N-Oxide and ^{15}N-Oxide in the present study (Table 1) was 1.41 and 1.93 mT, respectively. However, the similar biradical with the homogeneous moieties ^{14}N-Oxide and ^{14}N-Oxide in the aqueous solution yielded 4.8 mT (17.1GHz)[13]. The discrepancy is due to the interaction between ^{15}N-Oxide and ^{14}N-Oxide moieties, in other words isotope effects. The *J*-value in the present study was 13.6 MHz. This value is compared with 65 and 56 MHz in the similar biradical in the aqueous solution and in the SDS micelle solution, respectively [13]. The difference in the *J*-value might be attributable to the distance between the moieties.

5. Conclusions

1. Biradical compounds which differ in the direction and distance between their ^{14}N-Oxide and ^{15}N-Oxide moieties in the same molecule were generated, and a general composition method for an aromatic diamide type biradical compound was established.

2. From the ESR spectra of both the urea type and the aromatic diamide type biradical compound, the distance between the ^{14}N-Oxide and ^{15}N-Oxide moieties were checked and correlated with features of the ESR spectrum.
3. It is possible to perform distance measurements between N-Oxides from spectrum changes by measuring biradical compounds which differ in distance between their N-Oxide biracial by ESR.

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