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Synthesis and ESR behaviors of nitroxide monoradical based on calix[4]arene

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Abstract—A novel paramagnetic calix[4]arene **6** with an N–O monoradical on the upper rim was synthesized and studied by ESR spectroscopy. Its ESR behaviors were mainly induced by its intrinsic conformational flexibility. The effects of varying temperature and complexation of silver ions on its ESR behaviors were also investigated.

The covalent attachment of stable nitroxide radicals to specific sites on calixarenes could provide valuable information portraying the local environment and, in particular, about dynamic conformational transformations by the exchange interaction among different N–O radicals, such as the geometrical changes induced by complexation of metal ions to the cavity of lower rims functionalized with N–O radicals.[1] We firstly investigated the intramolecular spin–spin exchange interaction of two nitroxide radicals on the upper rims of calix[4]arene.[2] Magnetic studies of stable nitroxide tetraradicals on the upper rim of calix[4]arene, which were conformationally immobilized as a cone, were also reported.[3] But almost all these valuable information describing the local environment was afforded by intramolecular exchange interaction among different spin centers. Could a monoradical attached on calixarene provide any information about the local environment? Here we report the synthesis of a novel paramagnetic calix[4]arene with an N–O monoradical on the upper rim and its ESR behaviors on the conformational alternation and complexation of silver ion. We hope that the present study will provide potential to conformational research of heteroatom-bridged calixarenes in which the methylene bridges are replaced by heteroatoms such as S and O, whereas NMR studies on the bridging groups CH_2 are usually carried out for determining conformations of common calixarenes in solution.

Paramagnetic calix[4]arene **6** was prepared according to Scheme 1 with selective benzoyl-protected calix[4]arene **1**[4] as the precursor. Compound **5** was yielded through the halogen–lithium exchange reaction of **4** followed by the reaction with 2-methyl-2-nitrosopropane (MNP), and easily oxidized in solution upon exposing to air. Due to the instability of compound **5**, **5** was directly oxidized into the final product **6** for characterization. Compound **6** was obtained as a red powder through the phase-transfer oxidation of **5** with PbO_2 and characterized by ESI-MS, ^1H NMR, HPLC, and elemental analysis.

The ESR measurements of **6** were carried out in toluene at a high dilution. A typical symmetrical ESR spectrum of nitroxide monoradical was observed, as having a broad equivalent triplet at $g = 2.0058$ with a nitrogen hyperfine coupling constant $A_N = 14.4$ G. When the toluene solution of **6** was bubbled with nitrogen gas, another ESR splitting pattern (Fig. 1) of **6** was observed (similar to that in the degassed solution). There remained the triplet corresponding to nitrogen hyperfine coupling, but each broad peak of the triplet was split into three narrow peaks due to the hyperfine coupling of the two equivalent *ortho* hydrogen nuclei of the phenyl ring. However, a careful examination of the unsymmetrical ESR spectrum of **6** suggested that it was produced by superposition of at least two kinds of monoradical nine-line ESR spectra, in which one set of signals at $g = 2.0064$ was the major species with $A_N = 14.6$ G, $A_H = 1.5$ G and another set at $g = 2.0061$ was the minor species with $A_N = 13.0$ G, $A_H = 1.7$ G. This superposed ESR spectrum of **6** was

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Keywords: Calix[4]arene; Nitroxide radical; Conformation; ESR.

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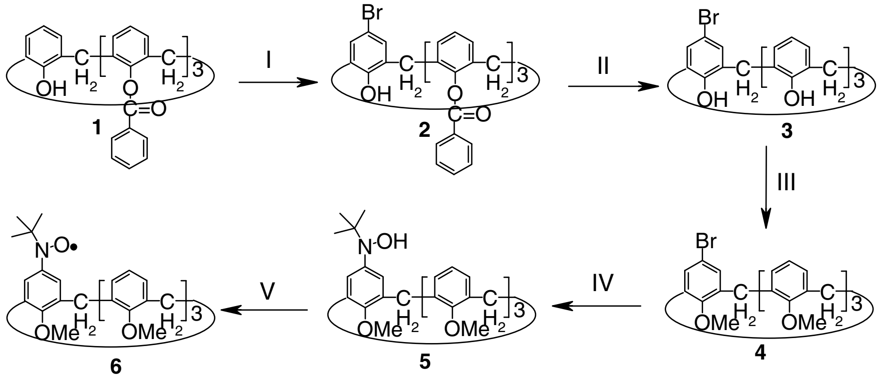

Scheme 1. The synthesis route of **6**. Reagents and yields: (I) Br_2, 90%; (II) NaOH, MeOH, THF, 98%; (III) CH_3I, THF, DMF, 68%; (IV) *n*-BuLi, 2-methyl-2-nitrosopropane (MNP); (V) PbO_2, benzene, 35% for (IV) and (V).

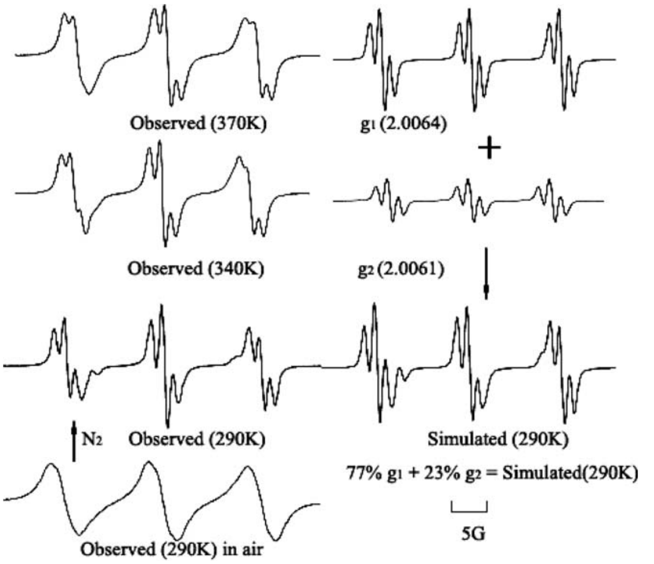

Figure 1. The ESR spectra in toluene under nitrogen at different temperatures and the simulated ESR spectrum at 290 K.

well simulated using the WINEPR program and the proportion of the major monoradical was estimated to be more than 75% (Fig. 1).

This phenomenon could be ascribed to the conformational mobility of **6**. The methoxy groups on the lower rims of **6** were too small to inhibit the oxygen-through-the-annulus rotation,[5] giving rise to a conformational equilibrium in solution between several discrete conformations. The variation of conformation caused a magnetic environment around the nitroxide radical to change, resulting in different ESR behaviors.

The ^1H NMR spectrum of **6** was broadened by paramagnetism of the radical and could not afford valuable information to distinguish among different conformations. But 1D and 2D NMR spectra of **4** in toluene-d_3 showed that calix[4]arene **4** adopted four kinds of discrete conformations in different percentages: cone (ca. 34.5%) and three partial-cone (ca. 65.5%) conformations.[6] The partial cone was the predominant conformation as reported by other conformational investigations of tetramethyloxycalix[4]arene.[2,7] As for line shapes of ^1H NMR spectra in $CDCl_3$, the CH_2 and CH_3O signals of **6** were very similar to those of **4** and both have the same molecular backbone other than the mono-substituted functional group. Then it could be deduced that the conformational distribution pattern of **6** was analogous to that of **4** to some extent. When calix[4]arene **6** exhibited a cone and two partial-cone conformations in which the nitroxide radical was placed above the bridging CH_2 mean plane, the N–O monoradical positioned in the magnetic atmosphere of phenyl rings corresponding to the major ESR signal at $g = 2.0064$. A small difference in the magnetic environment results in a small broadening of the ESR spectrum line which cannot be distinguished. However, the ESR signal at $g = 2.0061$ may arise from **6** in the third partial-cone conformation, in which the phenyl ring with the nitroxide monoradical pointed opposite of the other three phenyl rings. Thus, the two kinds of N–O monoradical ESR spectra overlapped on the observed ESR spectrum of **6** in toluene.

When the toluene solution of **6** was heated, the ESR signals of two different nitroxide monoradicals were enhanced and began to close up. As the solution was heated up to 370 K, the two ESR signals coalesced gradually. This suggested that conformational exchanges among the different conformational isomers of **6** were accelerated upon heating, the upside-down rotation of nitroxide radical along with the phenyl ring was also speeded up. The nitroxide radical experienced a fast transition of the magnetic environment between phenyl rings and methoxyl groups. The ESR spectra of **6** in 340 and 370 K were also simulated, in which the ratios of the two kinds of different N–O monoradical changed along with the increase of temperature.

The extraction of Ag^+ ion with a toluene solution of **6** from an aqueous $AgNO_3$ solution caused moderate changes in its ESR spectrum. This may suggest that the complexation of Ag^+ ion made the conformation of calix[4]arene **6** modified and the ratio of the two kinds of N–O monoradicals changed, leading its ESR signal to change. Furthermore, addition of an organic salt of silver ($AgNS_2C_5H_{10}$) directly into a dichloromethane

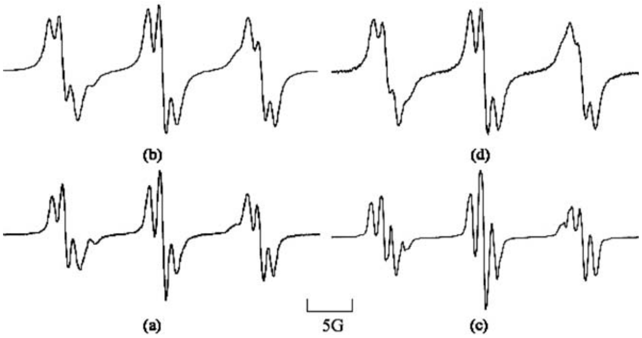

Figure 2. The ESR spectra of **6** in toluene before (a) and after (b) extracting the Ag^+ ion; the ESR spectra of **6** in CH_2Cl_2 before (c) and after (d) including the Ag^+ ion.

solution of **6** also caused a larger change on the ESR spectrum of **6** (Fig. 2), whereas addition of the same organic salt of zinc had almost no effect. This means calix[4]arene **6** has a selective complexation for Ag^+ ion, and may be used as a selective chemical sensor for the Ag^+ ion. To confirm this selective complexation, we made ESI-MS measurements on the complex solutions of Ag^+ and Zn^{2+} ions, respectively. Interestingly, there was a strong signal observed indicative of a calix[4]arene **6** including two Ag^+ ions (see Supplementary data), and no signal corresponding to the complex Zn^{2+} ion was detected. Although some investigations[8] on the complexation of an Ag^+ ion by a tetramethoxycalix[4]arene molecule have been reported, there are no findings about whether one analogous molecule of tetramethoxycalix[4]arene could include two Ag^+ ions. This may be attributed to the desirable conformation of **6**, but the exact reason for this is under investigation.

In conclusion, a novel paramagnetic calix[4]arene with an N–O monoradical was synthesized and studied by ESR spectroscopy. Although there are some investigations on ESR behaviors of paramagnetic calixarenes bearing an N–O multiradical, they all concern the spin–spin exchange interaction among different radical sites controlled by the metal-binding event[1] or reversible conformational transition.[2] The present ESR behaviors belong to the calixarene with an N–O monoradical and were mainly induced by its intrinsic conformational flexibility. It is reasonably anticipated that an ESR study on this kind of mono-spin labeled calixarenes may provide valuable basic concepts for the understanding of conformational transformations and exchange interaction between intermolecular radicals.

Supplementary data

Synthesis procedure for **6**, other ESR simulation data, NMR, and ESI-MS spectra. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.08.034. See http://www.sciencedirect.com.

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