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Synthesis and reversible thermo-induced conformational transitions of a stable nitroxide biradical based on calix[4]arene†

Qi Wang, Yong Li* and Guo-shi Wu
Department of Chemistry, Tsinghua University, Beijing 100084, P. R. China

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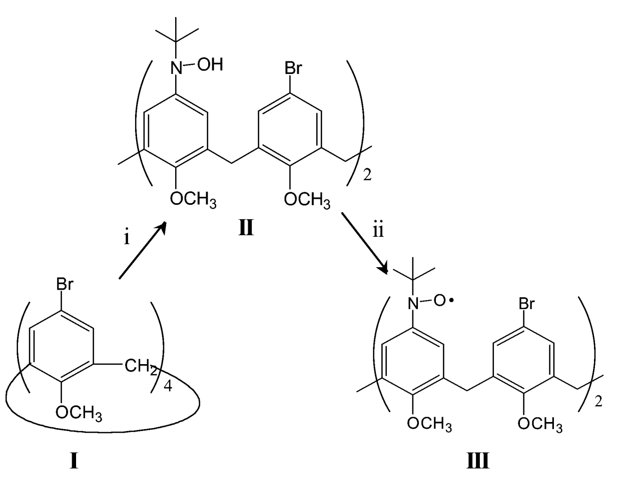
A stable paramagnetic calix[4]arene(III) bearing two nitroxide groups on the upper rim is synthesized, which exhibits a strong intramolecular spin–spin exchange interaction and is found to be able to undergo reversible conformational transitions upon heating.

Stable nitroxide free radicals have been widely used as spin labels and spin probes in various scientific and technical fields for many years.[1] The spin exchange interaction and dipolar interaction between different spin centers are usually sensitive to molecular structures, and generally provide valuable information about the local environment.[2] Shinkai *et al.*[3] and Ziessel *et al.*[4] have attached nitroxide groups to calixarenes, a class of versatile host molecule as well as promising building blocks used in novel supramolecular and macromolecular systems.[5,6] ESR (electron spin resonance) studies on these paramagnetic calixarenes revealed their marked potential in designing chemical sensors that are sensitive to metal cations. All the radical moieties were located on the lower rim of calixarene and relatively far from the cavity formed by the phenyl rings. Our interest was attracted by what would happen if multiple radicals were introduced directly onto the phenyl rings, such as in *N*-*tert*-butyl phenyl nitroxides, which have been developed as good coupler units of various magnetic compounds.[7] In fact, we have detected such compounds by spin trapping methods.[8] But unfortunately the spin-labelled molecules are difficult to separate. In the present study, a stable paramagnetic calix[4]arene functionalized by *N*-*tert*-butyl nitroxide on the upper rim is prepared and studied by ESR spectroscopy.

First, compound **II** was obtained through selective halogen–lithium exchange of 5,11,17,23-tetrabromotetramethoxycalix[4]arene (**I**) by *n*-BuLi, followed by reaction with 2-methyl-2-nitrosopropane (MNP) (Scheme 1).‡ Gutsche has reported that conformationally flexible calix[4]arenes such as compound **I** usually give complete halogen–lithium exchange.[9] However, in this case, selective Br–Li exchange was observed. According to the X-ray crystal structure analysis of **II**, the substitutions take place at the *para* positions of the two opposite phenyl rings and the calix[4]arene platform exhibits partial cone conformation.[10] Furthermore, as a result of intramolecular hydrogen bonds both hydroxyaminol groups are oriented inwards into the cavity of calix[4]arene. This is in good agreement with the ^{1}H NMR spectrum of **II** recorded in $CDCl_3$. And it is estimated by ^{1}H NMR analysis that over 90 percent of **II** displays the partial cone conformation in solution. After oxidation by PbO_2 the resultant nitroxide radical **III** was obtained as an orange oil . It was very stable in air even upon heating for a long time. The compounds were characterized by ^{1}H NMR, HPLC-MS, UV–Vis, IR and elemental analysis.§

ESR studies of **III** were carried out in toluene at high dilution. A typical spectrum of nitroxide biradical was observed at room temperature (Fig. 1a). From the ESR lineshape, the spectrum can be regarded as two sets of overlapping signals at g = 2.0067: a broad triplet with nitrogen hyperfine coupling constant A_N = 13.6 G and a quintet with A_N = 6.4 G, which corresponds to the coupling of two equivalent nitrogen nuclei. The spectrum was well simulated using WINEPR simfonia program (Fig. 1, the dashed line) and the proportion of the quintet was estimated to be more than 60 %. The five lines are



Scheme 1 Synthesis route of **III**. *Reagents*: i, *n*-BuLi, 2-methyl-2-nitrosopropane (MNP) in THF; ii, PbO_2 in benzene.

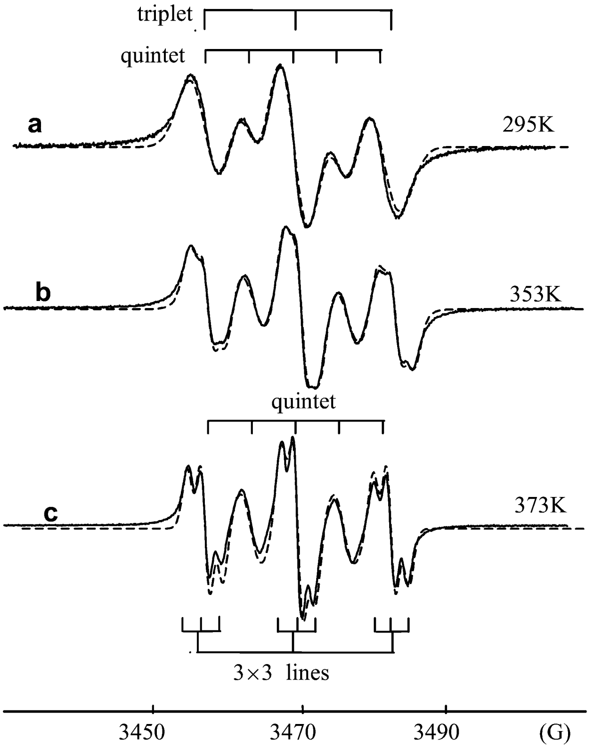


Fig. 1 ESR spectra of **III** in toluene at different temperatures (solid line — experimental spectra; dashed line — the best fits of simulation).§

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† Electronic supplementary information (ESI) available: selected experimental details. See http://www.rsc.org/suppdata/cc/b2/b201010k/

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a clear indication of strong spin–spin exchange interaction ($J >> A_N$), which can also be supported by the forbidden transition $\Delta M_S = \pm 2$ observed at 77 K at a field of 1675 G. These two kinds of spectra result from different states of **III** Fig. 2a, b). It is deduced that after oxidation, most of the calix[4]arenes maintain partial cone conformation with both of the two N–O$^\bullet$ groups pointing into the cavity. Thus the two radical parts are placed in proximity and are allowed to induce strong spin–spin exchange interaction (Fig. 2a), which results in a quintet. On the other hand, the elimination of hydrogen bonds helps phenyl rings and bulky *tert*-butyl groups to rotate more freely. The broad triplet lines may arise from such a conformation as shown in Fig. 2b, in which the two nitroxide subunits rotate to the outside leaving a longer distance to each other. In this case, through-space spin–spin exchange is blocked while the dipole–dipole interaction is still powerful enough to broaden the ESR lines.

Interestingly, reversible changes of ESR spectra induced by heating were observed. When a toluene solution of **III** was heated, no obvious changes were found below 353 K. However, above that temperature the ESR signals were enhanced and the triplet lines gradually split into 3 × 3 peaks (Fig. 1c), which are assignable to the hyperfine coupling of the two *ortho* hydrogen nuclei of the phenyl ring with $A_H = 1.8$ G. The proportion of the quintet was estimated by reasonable simulation as nearly half at 373 K.

Surprisingly, the spectrum did not return back to the original pattern as the hot solution was cooled down rapidly. Clear splittings remained for several hours and broad lines recovered quite slowly. This reversible change could be easily reproduced many times without destruction of the sample. These results support a view that under heating another stable conformational isomer of **III** showing an ESR signal of sharp 3 × 3 peaks is produced, in which the distance between the two radical parts is so long that neither spin–spin exchange nor dipole–dipole interaction is in effect. It is easily found that only when the two opposite phenyl rings bearing nitroxides are located in *anti* orientation, the biradical has the largest distance between the two radical parts. One can notice that a 1,2-alternate conformation (Fig. 2c), which can be generated from partial cone conformation through the upside-down rotation of one spin-labelled phenyl ring, completely satisfies this conformational requirement. It has also been reported that calix[4]arenes with bulky substituents at the *para* positions prefer to experience a conversion from partial cone to 1,2-alternate conformation at high temperature.[11–13] According to the above results, a reasonable mechanism of the conformational transition is proposed as shown in Fig. 2 and the 1,2-alternate conformation is generated as the temperature is elevated.†

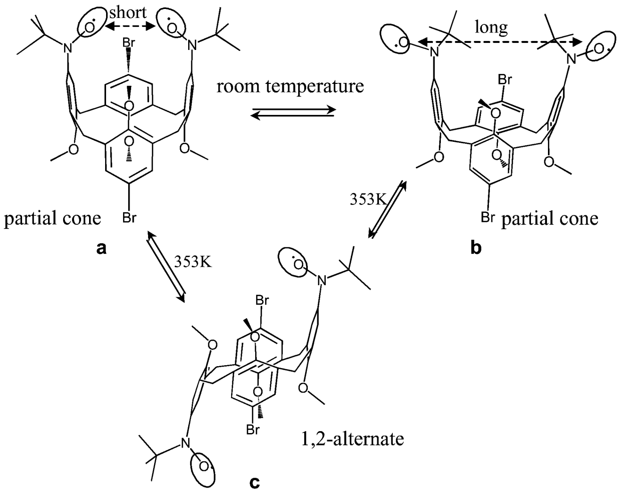

Fig. 2 Schematic representation of thermal-induced distance changes between nitroxide groups in different conformations of compound **III** (all of the above molecular structures have been optimized by MNDO calculation).

In conclusion, a stable paramagnetic calix[4]arene has been studied by ESR spectroscopy and a strong through-space spin–spin exchange interaction was found. Although similar spin interactions were also observed in previous studies,[3,4] they were regulated by adding metal cations and no reversible process was reported. In the present study, due to the peculiar flexibility of calixarenes, interesting conformational transitions are induced upon heating, which give rise to temperature-sensitive ESR observations. This process is fully reversible, and we believe that this thermal-magnetic effect may provide a valuable concept for the potential applications in designing functionalized calixarenes with novel magnetic properties.

Notes and references

‡ General experimental procedure and selected spectra. Compound **II**: *n*-BuLi (4.5 ml of a 1.6 M solution in hexanes, 7.20 mmol) was added dropwise to **I** (1.0 g, 1.25 mmol) in toluene at −78 °C under an atmosphere of N_2. After 1 h, 2-methyl-2-nitrosopropane (0.75 g, 8.62 mmol) in anhydrous THF was added. The reaction mixture was allowed to warm to ambient temperature overnight. After the usual workup, the resulting yellow oil was chromatographed on silica gel with benzene–methanol elution. The first constituent was collected and concentrated to give 0.30 g (30%) of **II** as white solids. After recrystallization from benzene colorless plates were obtained: mp 228–230 °C. Anal. Calcd for $C_{40}H_{48}N_2O_6Br_2$: C 59.1; H 5.95; N 2.87. Found: C 59.4; H 5.97; N 3.44%. ^{1}H NMR (200 MHz, $CDCl_3$, Me_4Si), partial cone: δ 9.10 (s, 2H, OH); 7.32–7.18 (m, 8H, ArH); 4.01 (d. $J = 14$, 2H, CH_2ArCH_2), 3.77 (d $J = 14$, 2H, $ArCH_2Ar$), 3.70 (m, 4H, CH_2ArCH_2), 3.68 (s, 6H, OCH_3), 3.55 (s, 3H, OCH_3), 2.94 (s, 3H, OCH_3); 1.08 (s, 18H, $(CH_3)_3C$). MS (ESI, *m/z*) $[M - 1]^-$: 809, 811, 813. IR(ν_{max}): 3240 cm^{-1} (br OH); 1388 cm^{-1} (s N–O). UV–vis ($CHCl_3$): 214, 300 nm. The oxidation of **II** was unavoidable during the reaction, which resulted in a relatively low yield.

Compound **III**: a benzene solution of **II** (20 mmol) was reacted with excess PbO_2 for over 1 h. After filtration, the solvent was removed and recrystallization from ether gave pure **III** as an orange oil: 80–82 °C. MS (ESI, *m/z*) $[M + e + 2H]^+$: 810, 812, 814. UV–vis: 240, 300, 380 nm. (The ^{1}H NMR spectrum was broadened by the radical species and therefore useless.)

§ Program WINEPR Simfonia, Bruker Analyltische Messtechnik Gmbh©, 1994–1996, Version 1.25.

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