Pergamon

Tetrahedron Letters, Vol. 37, No. 48, pp. 8755-8758, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)02042-4

Nitroxo Spin-Labelled Calix[4]arene Podands and Cryptands: Allosteric Regulation of Spin-Spin Exchange Interaction

Gilles Ulrich,[a] Philippe Turek*[b] and Raymond Ziessel*[a]

[a] *Ecole Chimie, Polymères, Matériaux, 1 rue Blaise Pascal, 67008 Strasbourg, France*
[b] *Institut Charles Sadron, Université Louis Pasteur, 6 rue Boussingault, 67083 Strasbourg, France*

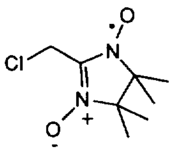
Key Words: paramagnetic sensors, nitroxyl radicals, calix[4]arene, calixspin, calixbipy, EPR detection

Abstract: Hybrid calix[4]arene podands and cryptands, each bearing two or four stable nitronyl-nitroxide radicals and two bipyridine subunits, exhibit through-space exchange interaction, the magnitude of which can be modulated by coordination of Zn^{2+} cations at the bipyridine sites.

Stable nitroxide free radicals are widely used as spin labels, as contrast-enhancing agents and as paramagnetic markers for EPR imaging spectroscopy.[1,2] These radicals have also attracted attention because of their ferromagnetic ordering at low temperature.[3] Furthermore, covalent attachment of organic radicals like TEMPO (2,2,6,6-tetramethyl-piperidinyl-1-oxyl) to specific sites on certain molecular receptors can provide valuable information describing the local environment and, in particular, about dynamic conformational exchange.[4,5] In solution the extent of intramolecular spin exchange and dipolar splitting in biradicals can be used as a sensitive probe for molecular structures, especially geometry changes induced upon binding of diamagnetic metal cations[6] and/or neutral substrates.[7] In almost all molecular systems reported to date the paramagnetic probe comprises a sterically-hindered TEMPO derivative.

We describe herein a synthetic rational for functionalization of calix[4]arenes with multiple nitronyl-nitroxide appendages. The latter are stable organic radicals with significantly less inherent steric crowding than TEMPO analogues and are subject to close-range spin-spin exchange interaction. The extent of this mutual coupling between radicals attached to the same molecular receptor should depend markedly upon molecular shape, size and flexibility, and should be susceptible to induced conformational modification. The approach described here allows easy access to macrocycles bearing different numbers of radical sites and additional chelating functions (compounds **2**-**5**). In such molecular architectures it might be anticipated that the level of spin-spin interaction between adjacent radicaloid species will reflect the presence of diamagnetic guest cations.

Specifically, paramagnetic calixarene-based sensors (*calix-spin* or *calix-bipy-spin*) grafted with two or four nitronyl-nitroxide radicals **2-5** (bipy = 2,2'-bipyridine) have been prepared in good yield. The radicaloid precursor **1** is prepared by condensation of 2,3-bis(hydroxyamino)-2,3-dimethylbutane[8] with chloroacetaldehyde, followed by phase-transfer oxidation with $NaIO_4$. Attachment of two or four such radicals to the calixarene core is accomplished by nucleophilic substitution in the presence of catalytic amounts of iodide (KI for **2** and NaI for **3-5**). Subsequent appendage of bipyridyl-based podands or cryptands,[9] giving rise to **4** and **5** respectively, retain the cone conformation (vide supra). All compounds were characterized by FAB^+, UV-Vis, IR and elemental analysis.[10] The number of free radical moieties in **2**-**5** was checked by room-temperature magnetic susceptibility measurements giving the expected product of molar susceptibility and temperature of 0.735 for **2**, 1.490 for **3**, 0.740 for **4** and 1.485 emu.K.mol^{-1} for **5**. These measurements showed the onset of intramolecular antiferromagnetic coupling below ca 10K and the magnetic properties over an extended temperature range (1.4 to 300K) could were well described in terms a Curie-Weiss law.



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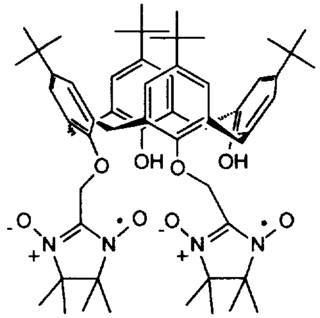

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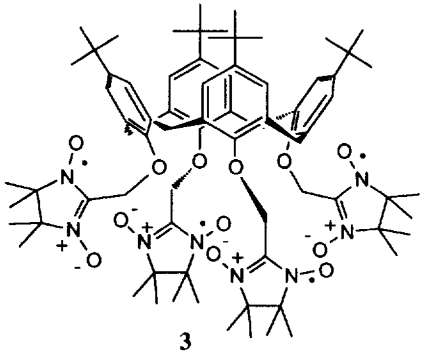

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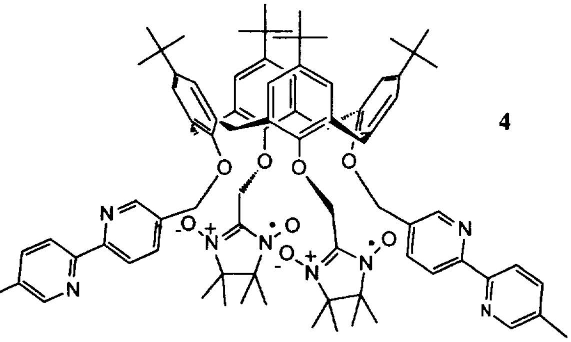

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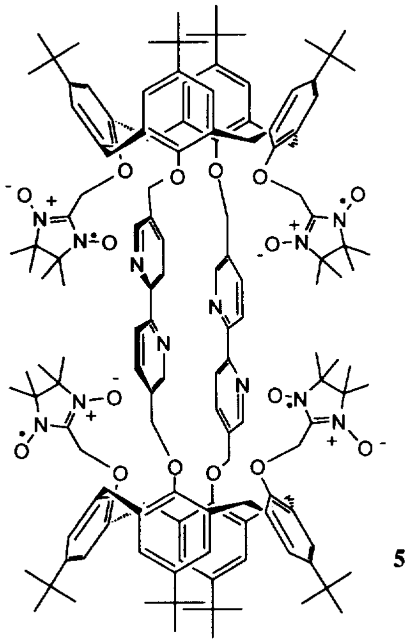
The capability of these molecules to function as diamagnetic cation sensors depends upon their adoption of well-defined conformation in solution and particular it is desirable that the calixarenes exist preferentially as cone conformers. This information can only be obtained from ^{1}H NMR spectroscopy of the reduced products. Clean reduction of **2**-**5** was achieved in methanol, under argon, using 0.5 equiv. of L-ascorbic acid.[11] Upon reduction **2** gave the characteristic ^{1}H NMR spectrum[12] of a 1,2-functionalized calix[4]arene, the structure of which was further authenticated by an X-ray diffraction study.[13] Reduction of **3**-**5** give products having the characteristic ^{1}H NMR spectra of cone conformers. Interestingly, the bridging CH_2-O group adjacent to the radical (δ = 5.3-5.6 ppm) was sufficiently acidic to facilitate rapid exchange with D_2O.

Compounds **2**-**5** were investigated by EPR under X-band irradiation in degassed dichloromethane/toluene 1:1 at high dilution. For **4**, the observed nine-line EPR spectrum (Fig. 1a) is readily ascribed to the hyperfine coupling of four equivalent nitrogen nuclei ($a_N \approx 3.60$ G). This finding is a clear indication of through-space spin-exchange interaction between the two nitroxo subunits. The unresolved hyperfine pattern superimposed on the main lines of the spectrum corresponds to coupling with the equivalent hydrogen nuclei ($a_H \approx 1.10$ G) at the α position of the nitroxo moieties. Coordination of a Zn^{2+} cation at room temperature to the vacant bipy sites available in **4** causes collapse of the nine-line spectrum (Fig. 1b).[14] The resultant EPR spectrum has only five major lines, which we consider to indicate a marked decrease in the extent of spin-spin interaction as would result from increased spatial separation of the radicals. Thus, the primary effect of cation complexation is to force apart the radicaloid subunits. Addition of smaller cations (Li^+, Na^+ or K^+), which have less affinity for binding to the bipy units, has little if any effect on the EPR spectrum recorded for **4**. Close examination of Fig. 1b, however, suggests that there is a small residual coupling between the radicals which might arise from dynamic equilibration among the various species.



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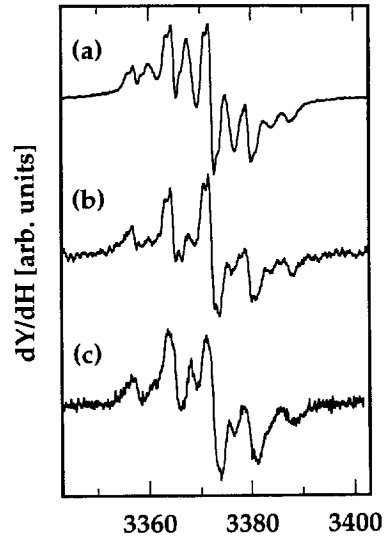

Figure 1. Room temperature EPR spectra of a 1/1 dichloromethane/toluene solution (10^{-4} M) of: (a) diradical **4**; (b) diradical **4** in the presence of Zn^{2+} ion; (c) tetraradical **5**. Abscissa: magnetic field in gauss.

Surprisingly, EPR spectra recorded for **2**, with or without added cation, show no pronouced spin-spin exchange interactions between the radicals. This may indicate restricted conformational mobility, as is clearly apparent from the solid state structure. The EPR spectrum of **3** exhibits obvious spin coupling between the four nitroxo radicals but unlike **4** is not perturbed by the presence of cations. The spectrum of **5** (Fig. 1c) resembles that recorded for **4** in the presence of Zn^{2+} (Fig. 1b). It is concluded that the rigid and enlarged structure of **5** prevents close contact between the nitroxo radicals, thereby restricting spin-spin exchange to a low level. As expected for this compound, addition of Zn^{2+} has no effect on the observed EPR spectrum.[14]

In conclusion, a new family of spin-labelled sensors has been introduced that contain discrete binding sites for both diamagnetic cations and neutral substrates. Excluding **2** where the radical sites lie in close proximity, spin-spin interaction between neighbouring radicals is observed by room-temperature EPR spectroscopy. Comparison of **2** to **4** suggests that optimal interaction occurs between radicals located at the 1,3-distal position on the lower rim of the calixarene. This interaction can be broken by insertion of an appropriate cation into the available coordination sites. In such cases spin-spin coupling is observed only for uncomplexed podand sensors, permitting quantitative determination of in-situ diamagnetic metal cations. Control experiments with **3** indicate clearly that non-complexed cations do not disrupt spin-spin coupling while for the cryptand-based sensor **5**, complexation of cation in the central cavity does not induce spin-spin interaction. Therefore *calix-bipy-spin* sensors such as **4** possess the correct geometry for both maximum interaction between the radicals and regulation of spin-spin exchange by adventitious cations which are otherwise difficult to detect. It is anticipated that improved systems might result from optimization of extracavity coordination sites such that specific complexation could occur while additional sensors might be able to monitor entrapment of a diamagnetic guest within the calixarene intracavity.

References and Notes

1 *Synthetic Chemistry of Nitroxides*, eds L. B. Volodarsky, V. A. Reznikov, V. I. Ovcharenko, CRC Press, 1994.

2 Swartz, H. M.*Pure & Appl. Chem.*, **1990**, *62*, 235-239; Likhtenstein, G. I. *Pure & Appl. Chem.*, **1990**, *62*, 281-288.

3 Chiarelli, R.; Novak, M. A. Tholence, J. L.; Rassat, A. *Nature*, **1993**, *363*, 147-149; Romero, F. M.; Ziessel, R.; Drillon, M.; Tholence, J.-L.; Paulsen, C.; Kyritsakas N.; Ficher, J. *Advanced Materials*, **1996**, under press.

4 Kirschner, J. J.; Hustedt, E. J.; Robinson, B. H.; Hopkins, P. B. *Tetrahedron Lett.* **1990**, *31*, 593-596.

5 Araki, K.; Nakamura, R.; Otsuka, H.; Shinkai, S. *J. Chem. Soc., Chem. Commun.*, **1995**, 2121-2122.

6 Gagnaire, G.; Jeunet, A.; Pierre, J.-L. *Tetrahedron Lett.* **1989**, *30*, 6507-6510.

7 Gagnaire, G.; Jeunet, A.; Pierre, J.-L. *Tetrahedron Lett.* **1991**, *32*, 2021-2024.

8 Ullman, E. F.; Osiecki, J. H.; Boocock, G. B.; Darcy, R. *J. Am.Chem. Soc.* **1972**, *94*, 7049-7059.

9 Ulrich, G.; Ziessel, R. *Tetrahedron Lett.*, **1994**, *35*, 6299-6302.

10 **Synthesis and selected data**. Compound **2**: 78%; FAB m/z 986 $[M{+}e{+}2H]^+$, λ 541 nm, ε 780 $M^{-1}cm^{-1}$ ($n \rightarrow \pi^*$); IR (KBr pellets, cm^{-1}) 3343 (ν_{OH}), 1374 cm^{-1} (ν_{NO}); Anal. Calc. for C, 72.99; H, 8.32; N, 5.67; Found C, 72.91; H, 8.28; N, 5.54; Compound **3**: 18%; FAB m/z 1329 $[M{+}4e{+}5H]^+$, UV-Vis. λ 542 nm, ε 2900 $M^{-1}cm^{-1}$ ($n \rightarrow \pi^*$); IR 1373 cm^{-1} (ν_{NO}); Anal. Calc. for C, 68.85; H, 8.21; N, 8.45; Found C, 68.63; H, 8.07; N, 8.30; Compound **4**: 52%; FAB m/z 1353 $[M{+}e{+}2H]^+$, UV-Vis. λ 543 nm, ε 1300 $M^{-1}cm^{-1}$ ($n \rightarrow \pi^*$); IR 1373 cm^{-1} (ν_{NO}); Anal. Calc. for C, 74.64; H, 7.61; N, 8.29; Found C, 74.58; H, 7.49; N, 8.17; Compound **5**: 40%; FAB m/z 2336 $[M{+}2e{+}3H]^+$, UV-Vis. λ 543 nm, ε 1730 $M^{-1}cm^{-1}$ ($n \rightarrow \pi^*$); IR 1372 cm^{-1} (ν_{NO}); Anal. Calc. for C, 74.07; H, 7.77; N, 7.20; Found C, 73.86; H, 7.57; N, 7.90.

11 Sosnovsky, G.; Konieczny, M. *Synthesis*, **1977**, 619-622.

12 **Selected ^{1}H NMR data for the L-ascorbic acid reduced 2-5 compounds**. For **2**: ^{1}H NMR (200MHz, $CDCl_3$) δ 5.35 (s, 4H, rad-$C\underline{H}_2$-O), 4.3-3.3 (3 AB quartets, 8H, J_{AB}=12 Hz, Ar-$C\underline{H}_2$-Ar calix), 1.25 (s, 18H, *t*-butyl), 0.90 (s, 18H, *t*-butyl); for **3**: δ 5.40 (s, 8H, rad-$C\underline{H}_2$-O), 3.85 (AB quartet, 8H, J_{AB}=12 Hz, Δν= 240 Hz, Ar-$C\underline{H}_2$-Ar calix), 1.20 (s, 36H, *t*-butyl); for **4**: δ 5.57 (s, 4H, rad-$C\underline{H}_2$-O), 5.12 (s, 4H, bpy-$C\underline{H}_2$-O), 3.65 (AB quartet, 8H, J_{AB}=12 Hz , Δν= 260 Hz, Ar-$C\underline{H}_2$-Ar calix), 1.26 (s, 18H, *t*-butyl), 0.80 (s, 18H, *t*-butyl); for **5** : δ 5.36 (s, 4H, rad-$C\underline{H}_2$-O), 5.16 (s, 4H, bpy-$C\underline{H}_2$-O), 4.75 (AB quartet, 8H, J_{AB}=12 Hz , Δν= 250 Hz, Ar-$C\underline{H}_2$-Ar calix), 1.28 (s, 18H, *t*-butyl), 0.96 (s, 18H, *t*-butyl).

13 Crystal data for **2**: $C_{60}H_{80}N_4O_8$, M_r = 985.3, monoclinic, space group $P2_1/c$, a = 19.623(6), b = 13.788(4), c = 22.829(7) Å, b = 109.23(2)°, Z = 4 (Kyritsakas, N.; DeCian, A.; Fischer, J. personnal communication).

14 FAB positive mode obtained for a methanol solution of **4** with $Zn(ClO_4)_2 \cdot 6H_2O$: 1515 $[\mathbf{4}{+}Zn{+}ClO_4]^+$, 1416 $[\mathbf{4}{+}Zn]^+$; or for a methanol solution of **5** with $Zn(ClO_4)_2 \cdot 6H_2O$: 2498$[\mathbf{5}{+}Zn{+}ClO_4]^+$, 2399 $[\mathbf{5}{+}Zn]^+$.

(*Received in France* 12 *September* 1996; *accepted* 16 *October* 1996)