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Nitric Oxide Release Mediated by Calix[4]hydroquinones

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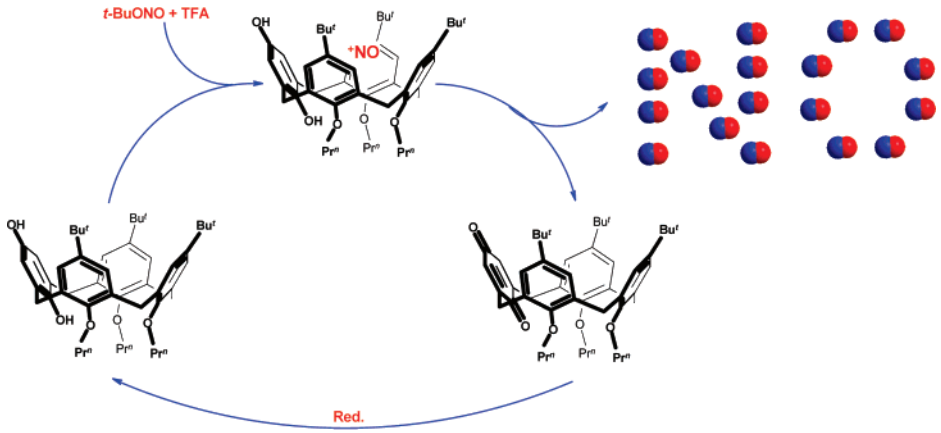
ABSTRACT



Calix[4]monohydroquinone has been used as a supramolecular system for the generation of NO gas. In a one-electron reduction scheme involving $NO^+\subset$calix[4]monohydroquinone complex, NO is released without the presence of an external reducing agent. Free calix[4]monoquinone, thus obtained, can be reused for a new NO-releasing cycle after $NaBH_4$-reduction to calix[4]monohydroquinone.

Nitric oxide (NO) is a colorless odorless gas, which plays important roles in several biological functions.[1] In particular, in the human body nitric oxide is involved in the regulation of cardiovascular, respiratory, and nervous systems. The development of therapeutic agents designed to release NO is an intensively active area of research, since NO gas has shown beneficial effects against several types of disease states. Thus, NO-releasing organic nitrates, as glyceryltrinitrate, are used as antianginal drugs[2] thanks to the vasodilatator properties of NO gas, whereas the antiinflammatory properties of NO gas have been used in NO-NSAIDS,[3] a class of nonsteroidal antiinflammatory drugs able to release NO. In addition, NO gas has shown antibacterial[4] and antitumoral[5] activity, and consequently, there is a strong

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(1) (a) Marletta, M. A.; Tayeh, M. A.; Hevel, J. M. *BioFactors* **1990**, *2*, 219. (b) Moncada, S.; Higgs, A. *N. Engl. J. Med.* **1993**, *30*, 2002. (c) Pfeiffer, S.; Mayer, B.; Hemmens, B. *Angew. Chem., Int. Ed.* **1999**, *38*, 1714. c) Fleming, I.; Busse, R. *Angew. Chem., Int. Ed.* **1999**, *31*, 5. (d) Ignarro, L. J. *Nitric Oxide: Biology and Pathobiology*; Academic Press: San Diego, CA, 2000. (e) Butler, A. R.; Nicholson, R. *Life, Death and Nitric Oxide*; Royal Society of Chemistry: Cambridge, 2003.

(2) (a) Murrell, W. *Lancet* **1879**, *1*, 80. (b) Parker, J. O.; Farrell, B.; Lahey, K. A.; Moe, G. *N. Engl. J. Med.* **1987**, *316*, 1635.

(3) Cirino, G. *Digestive and Liver Disease* **2003**, *35*, S2 and reference cited therein.

(4) (a) Albina, J. E.; Reichner, J. S. *Cancer Metastasis Rev.* **1998**, *17*, 19. (b) Nablo, B. J.; Chen, T.-Y.; Schoenfisch, M. H. *J. Am. Chem. Soc.* **2001**, *123*, 9712.

(5) (a) Cobbs, C. S.; Brenman, J. E.; Aldape, K. D.; Bredt, D. S.; Israel, M. A. *Cancer Res.* **1995**, *55*, 727. (b) Jenkins, D. C.; Charles, I. G.; Thomsen, L. L.; Moss, D. W.; Holmes, L. S.; Baylis, S. A.; Rhodes, P.; Westmore, K.; Emson, P. C.; Moncada, S. *Proc. Natl. Acad. Sci. U.S.A.* **1995**, *92*, 4392. (c) Thomsen, L. L.; Miles, D. W.; Happerfield, L.; Bobrow, L. G.; Knowles, R. G.; Moncada, S. *Br. J. Cancer* **1995**, *72*, 41.

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interest in the search of synthetic compounds that chemically store and release NO in a controlled fashion.[6]

Thus, Schoenfisch and co-workers have reported the synthesis and characterization of NO-releasing systems based on diazeniumdiolate[7] NO-donors.[8] The diazeniumdiolate groups, covalently bound to dendrimer or silica nanoparticles, were able to dissociate spontaneously under physiological conditions to give NO gas.

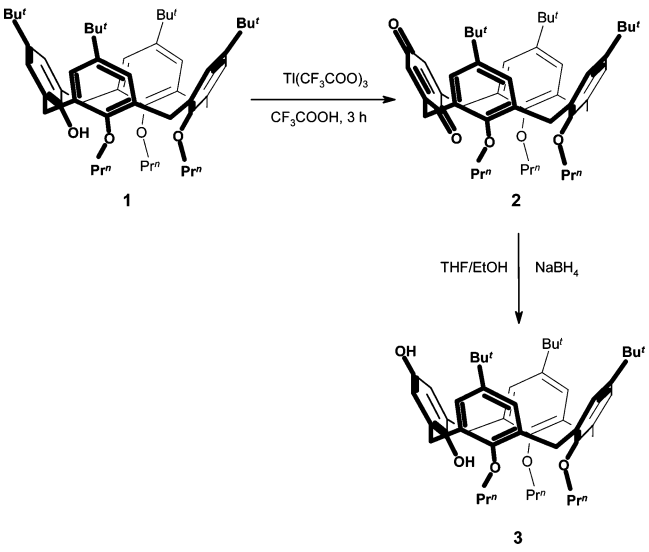
At the same time, there has been a growing interest in *supramolecular* systems that have the capability to reversibly trap, store, and release NO.[9,10] Among them, increasing attention has been devoted to the development of calixarene-based[11] materials able to store NO in the form of entrapped nitrosonium (NO^+) ion.[12] Thus, Rathore and Rudkevich have described stable complexes between calixarene derivatives and NO^+ ion,[12] with this ion strongly bound within the calixarene aromatic cavity by means of cation-π interactions.[13] This work was also extended to the storage of NO^+ ion into the cavity of synthetic calixarene-based nanotubes.[14,15]

We have shown that nitric oxide (NO) can be smoothly released from the calixarene cavity after a one-electron reduction scheme involving $NO^+\subset$calixarene complexes and an external reducing agent such as hydroquinone molecule.[16] After releasing NO, the starting calixarene was regenerated in 95% yield and was reused for a new NO-releasing cycle.

In this paper, we wish to report a new calixarene-based supramolecular system endowed with an internal hydroquinone reducing moiety and therefore able to release NO without the addition of external agents.

The designed compound, *p-tert*-butylcalix[4]monohydroquinone **3**, was obtained by $NaBH_4$ reduction of the corresponding tripropoxycalix[4]monoquinone **2**,[17] which in turn was prepared by $Tl(CF_3COO)_3$-mediated oxidation[18] of tripropoxy-*p-tert*-butylcalix[4]arene **1** (Scheme 1).[19,20]

Scheme 1



Examination of its ^1H and ^{13}C NMR spectra[20] indicated that calix[4]monohydroquinone **3** adopts a cone conformation.[21] In fact, two AX systems relative to $ArCH_2Ar$ groups [4.32/3.17 ppm (J = 12.5 Hz), 4.36/3.16 ppm (J = 13.2 Hz)] were present in the ^1H NMR spectrum (Figure 1a), whereas the ^{13}C NMR spectrum displayed two $ArCH_2Ar$ resonances at 31.2 and 31.4 ppm.[21c,d,22]

Tripropoxycalix[4]monoquinone **2** shows the presence of a broad singlet (or a very tight AB system) at 3.51 ppm relative to $ArCH_2Quin$ protons adjacent to quinone ring and an AX system [4.14/3.10 ppm (J = 12.5 Hz), 4H] relative to $ArCH_2Ar$ protons (see for comparison its spectrum in the presence of TFA reported in Figure 1d). This is indicative of a fixed *syn* orientation of ArOPr rings associated to a fast *through-the-annulus* rotation of the quinone ring. This behavior was confirmed by the presence of two resonances at 35.5 and 31.0 ppm relative to $ArCH_2Quin$ and $ArCH_2Ar$ carbon, respectively, in the ^{13}C NMR spectrum of **2**.[20,21c−d,22]

When *tert*-butylnitrite (2 equiv) was added to a mixture of calix[4]monohydroquinone **3** and TFA in $CDCl_3$, a deep-

(6) (a) Wang, P. G.; Xian, M.; Tang, X.; Wu, X.; Wen, Z.; Cai, T.; Janczuk, A. J. *Chem. Rev.* **2002**, *102*, 1091. (b) Burgaud, J.-L.; Onigini, E.; Del Soldato, P. *Ann. N. Y. Acad. Sci.* **2002**, *962*, 360. (c) Low, S. Y. *Mol. Aspects Med.* **2005**, *26*, 97. (d) Wang, P. G.; Cai, T. B.; Taniguchi, N. *Nitric Oxide Donors: For Pharmaceutical and Biological Applications*; Wiley-VCH: Weinheim, Germany, 2005.

(7) Hrabie, J. A.; Keefer, L. K. *Chem. Rev.* **2002**, *102*, 1135.

(8) (a) Stasko, N. A.; Schoenfisch, M. H. *J. Am. Chem. Soc.* **2006**, *128*, 8265. (b) Shin, J. H.; Metzger, S. K.; Schoenfisch, M. H. *J. Am. Chem. Soc.* **2007**, *129*, 4612.

(9) (a) Ding, X. D.; Weichsel, A.; Andersen, J. F.; Shokhireva, T. K.; Balfour, C.; Pierik, A. J.; Averill, B. A.; Montfort, W. R.; Walker, F. A. *J. Am. Chem. Soc.* **1999**, *121*, 128. (b) Padden, K. M.; Krebs, J. F.; MacBeth, C. E.; Scarrow, R. C.; Borovik, A. S. *J. Am. Chem. Soc.* **2001**, *123*, 1072. (c) Mitchell-Koch, J. T.; Reed, T. M. A.; Borovik, S. *Angew. Chem., Int. Ed.* **2004**, *43*, 2806.

(10) For a more general review on the supramolecular chemistry of gases, see: Rudkevich, D. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 558.

(11) For general reviews on calixarenes, see: (a) Böhmer, V. *Angew. Chem., Int. Ed.* **1995**, *34*, 713. (b) Ikeda, A.; Shinkai, S. *Chem. Rev.* **1997**, *97*, 1713. (c) Gutsche, C. D. *Calixarenes Revisited*; Royal Society of Chemistry: Cambridge, 1998. (d) *Calixarenes 2001*; Asfari, Z., Böhmer, V., Harrowfield, J., Vicens, J., Eds.; Kluwer: Dordrecht, 2001. (e) Böhmer, V. In *The Chemistry of Phenols*; Rappoport, Z., Ed.; Wiley: Chichester, UK, 2003; Chapter 19. (f) *Calixarenes in the Nanoworld*; Vicens, J., Harrowfield, J., Eds.; Springer: Dordrecht, 2006.

(12) (a) Rathore, R.; Lindeman, S. V.; Rao, K. S. S. P.; Sun, D.; Kochi, J. K. *Angew. Chem., Int. Ed.* **2000**, *39*, 2123. (b) Zyryanov, G. V.; Kang, Y.; Rudkevich, D. M. *J. Am. Chem. Soc.* **2003**, *125*, 2997. (c) Kang, Y.; Zyryanov, G. V.; Rudkevich, D. M. *Chem.−Eur. J.* **2005**, *11*, 1924.

(13) For a recent example of $NO^+\subset$resorc[4]arene complexes, see: Botta, B.; D'Acquarica, I.; Delle Monache, G.; Nevola, L.; Tullo, D.; Ugozzoli, F.; Pierini, M. *J. Am. Chem. Soc.* **2007**, *129*, 11202.

(14) Organo, V. G.; Leontiev, A. V.; Sgarlata, V.; Dias, H. V. R.; Rudkevich, D. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 3043.

(15) For a review on the host-guest chemistry of synthetic nanotubes, see: Organo, V. G.; Rudkevich, D. M. *Chem. Commun.* **2007**, 3891.

(16) Wanigasekara, E.; Leontiev, A. V.; Organo, V. G.; Rudkevich, D. M. *Eur. J. Org. Chem.* **2007**, 2254.

(17) Lu, L.-G.; Li, G.-K.; Peng, X.-X.; Chen, C.-F.; Huang, Z.-T. *Tetrahedron Lett.* **2006**, *47*, 6021.

(18) Reddy, P. A.; Kashyap, R. P.; Watson, W. H.; Gutsche, C. D. *Isr. J. Chem.* **1992**, *32*, 89.

(19) Iwamoto, K.; Araki, K.; Shinkai, S. *J. Org. Chem.* **1991**, *56*, 4955.

(20) See the Supporting Information for additional details.

(21) (a) Gutsche, C. D. Calixarenes; Royal Society of Chemistry: Cambridge, 1989, pp. 110−111. (b) Kanamathareddy, S.; Gutsche, C. D. *J. Org. Chem.* **1992**, *57*, 3160. (c) Bifulco, G.; Gomez-Paloma, L.; Riccio, R.; Gaeta, C.; Troisi, F.; Neri, P. *Org. Lett.* **2005**, *7*, 5757. (d) Bifulco, G.; Riccio, R.; Gaeta, C.; Neri, P. *Chem.−Eur. J.* **2007**, *13*, 7185.

(22) (a) Jaime, C.; de Mendoza, J.; Prados, P.; Nieto, P. M.; Sanchez, C. *J. Org. Chem.* **1991**, *56*, 3372. (b) Magrans, J. O.; de Mendoza, J.; Pons, M.; Prados, P. *J. Org. Chem.* **1997**, *62*, 4518.

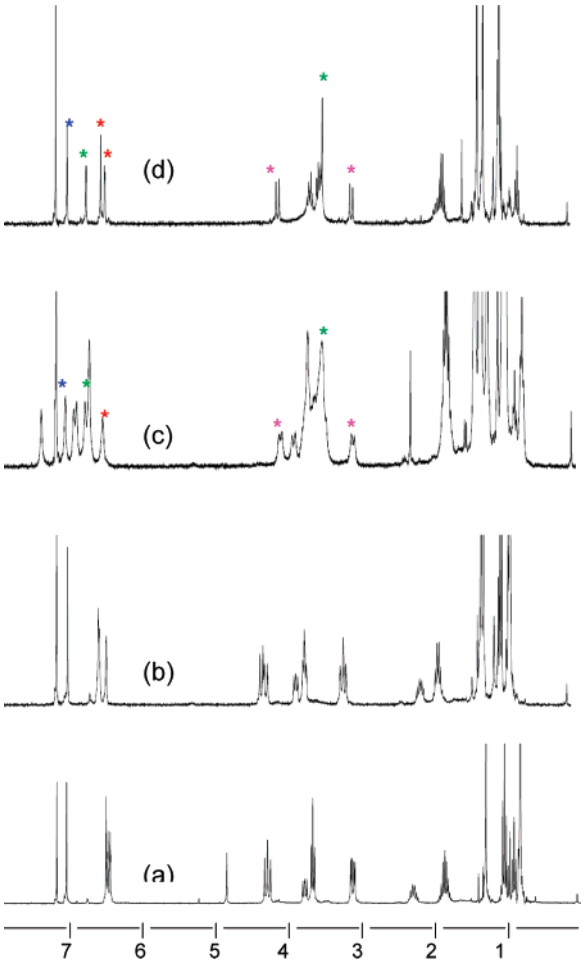


Figure 1. ^{1}H NMR spectra (300 MHz, $CDCl_3$, 295 K) of: (a) *p-tert*-butylcalix[4]monohydroquinone **3**; (b) monohydroquinone **3** in the presence of TFA; (c) formation of $NO^+\subset$**3** complex upon addition of *t*-BuONO to solution "b"; (d) Solution "c" after 5 min from the addition of *t*-BuONO, corresponding to monoquinone **2** in the presence of TFA. Relevant signals of monoquinone **2** are marked with asterisks in "c" and "d".

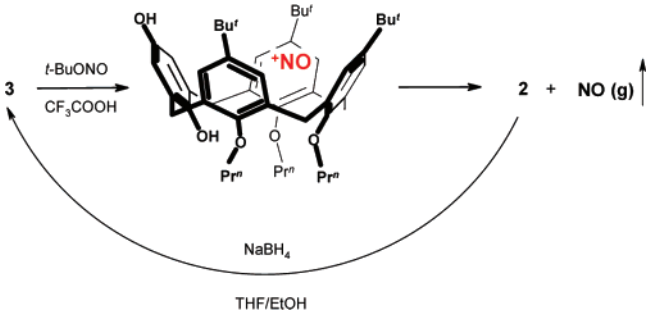
purple color initially appeared.[20] Subsequently, NO gas was released out from the system, and within 5 min, the solution turned to a transparent pale-yellow color.[23]

These results are consistent with an initially formed NO^+ ion encapsulated into the calixarene cavity and then quickly reduced to NO by means of a one-electron reduction scheme by the hydroquinone moiety of calix[4]monohydroquinone **3**, which was oxidized to calix[4]monoquinone **2**. Clearly, there are two possibilities for the reduction of NO^+ ion to NO: the first is an encapsulated π-complex, with NO^+ situated inside the calix[4]monohydroquinone cavity, whereas the second postulates an external π-complex, with NO^+ situated outside the calixarene cavity. Energetically, the encapsulated π-complex seems much more favorable; in fact, it is well known that NO^+ is easily encapsulated into the π-electron rich calix cavity and generally shows $K_{assoc} \gg 10^6$ M^{-1}.[12b] The deep-purple color initially developed is an additional proof of the formation of $NO^+\subset$**3** complex. In fact, as shown in previous works,[12,16] this deep-purple color is caused by the strong charge transfer interaction between NO^+ and the electron rich π-surface of aromatic rings present in **3**.[13] This was corroborated by a broad charge-transfer band at $\lambda_{max} = 545$ nm in $CHCl_3$, typical for these systems.[20,24]

^{1}H NMR analysis confirmed the above conclusions. In fact, the ^{1}H NMR spectrum of the mixture of *p-tert* butylcalix[4]monohydroquinone **3** and TFA (Figure 1b) changed substantially after the addition of *tert*-butylnitrite.

In particular, a new set of resonances relative to $NO^+\subset$**3** complex (Figure 1c) appeared, whose aromatic protons were shifted downfield with respect to calix[4]monohydroquinone **3**, in accordance with our previous results.[14,16] In addition, the ^{1}H NMR spectrum (Figure 1c) displayed also the resonances relative to tripropoxycalix[4]monoquinone **2** (marked signals). After that the reduction had taken place completely and neutral NO molecule was released, calix[4]-monoquinone **2** was obtained in quantitative yield, as confirmed by NMR analysis (Figure 1d) and by the transparent pale-yellow color of solution. Calix[4]monoquinone **2** thus obtained was sufficiently pure (Figure 1d) and, after $NaBH_4$-reduction to **3**, can be reused for a new NO-releasing cycle (Scheme 2).

Scheme 2



The headspace NO gas generated by the reaction between **3** and *tert*-butylnitrite in TFA was analyzed using UV spectrophotometry, and three characteristic peaks were obtained at $\lambda_{max} = 206$, 214, and 226 nm (Figure 2). These UV data are in agreement with previously published UV absorption data for identification of NO.[25]

In contrast to the NO-releasing experiment reported in Scheme 2, if 4 equiv of *tert*-butylnitrite were added to a

(23) In a preparative procedure, *tert*-butylnitrite (0.70 mmol) was reacted with trifluoroacetic acid (3.5 mmol) in presence of *p-tert*-butyl-calix[4]-mono-hydroquinone **3** (0.25 g, 0.35 mmol) in dry chloroform (1.5 mL) under vigorous stream of N_2. The evolved NO gas (ca. 7.6 mL, 0.34 mmol) was collected by a syringe or over cold water and identified by UV spectroscopy (yield 97%). Three characteristic peaks were observed at λ_{max} 206, 214, 226 nm, which confirmed the evolution of pure NO gas. The tripropoxycalix-[4]monoquinone **2** was quantitatively (>95%) produced and identified by ^{1}H NMR spectroscopy.

(24) (a) Borodkin, G. I.; Shubin, V. G. *Russ. Chem. Rev.* **2001**, *70*, 211. (b) Zyryanov, G. V.; Rudkevich, D. M. *J. Am. Chem. Soc.* **2004**, *126*, 4264.

(25) (a) Marmo, F. F. *J. Opt. Soc. Am.* **1953**, *43*, 1186. (b) Bosch, E.; Rathore, R.; Kochi, J. K. *J. Org. Chem.* **1994**, *59*, 2229.

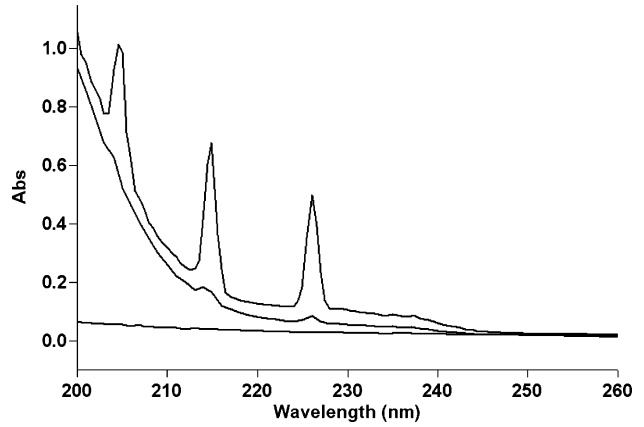
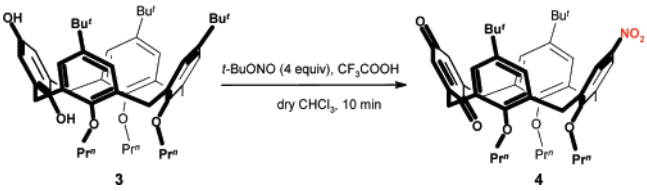


Figure 2. UV spectrum of the head space gas generated from the $NO^+ \subset$**3** complex.

mixture of **3** and TFA (10 equiv) in dry chloroform, the excess nitrosonium ion reacted further with calix[4]-monoquinone **2** and allowed the selective *ipso*-nitration of **2** at the distal aromatic ring with respect to the quinone moiety, yielding **4** in 60% yield (Scheme 3). The reaction

Scheme 3



outcome is likely to be the result of an initial *ipso*-nitrosation of **2**, followed by an oxidation of the nitroso intermediate to nitroderivative **4** by oxygen.[26] The structure of **4** was assigned by spectral analysis. In particular, the presence of a pseudo-molecular ion peak at *m*/*z* 723 in the ESI(+) mass spectrum confirmed the molecular formula. The molecular structure of **4** was confirmed by the pertinent signals in the ^{1}H NMR spectrum. In fact, a singlet was present at 8.07 ppm relative to protons in *ortho* to nitro group, whereas an AB system relative to the remaining aromatic protons was present at 6.54 and 6.89 ppm (J = 2.1 Hz, 4 H). In addition, a resonance was present at 6.74 ppm (2H) relative to the protons of the quinone moiety. Also in this case, the presence of a broad singlet at 3.56 ppm and of an AX system at 4.22/3.27 ppm (J = 13.0 Hz) relative to $ArCH_2Quin$ and $ArCH_2Ar$ protons, respectively, were indicative of a fast *through-the-annulus* rotation of the quinone ring of **4**, which was confirmed by the pertinent ^{13}C NMR signals.

The regiochemical outcome of the nitrosation can be explained by considering that very likely the excess NO^+ ion is complexed by quinone **2**, as indicated by the deep-purple color of the solution. In this complex, the nitrosonium cation should be sandwiched between the two distal Ar−OPr rings, which would be parallel to one another. In this way, the NO^+ ion is perfectly oriented to give the *ipso*-nitrosation onto the central Ar−OPr ring opposite to quinone system, with high regioselectivity.[27] This reaction can be considered as an interesting example of supramolecular control of a reaction outcome,[28] which could be probably exploited in a larger context.

In conclusion, we have shown that *p*-*tert*-butylcalix[4]-monohydroquinone **3** can be used for the generation of NO gas. In a one-electron reduction scheme involving $NO^+ \subset$**3** complex, NO is released without the presence of an external reducing agent. Free tripropoxycalix[4]monoquinone **2**, thus obtained, can be reused for a new NO-releasing cycle after $NaBH_4$-reduction to **3**.

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Supporting Information Available: Experimental and synthetic details and ^{1}H/^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(26) For spontaneous oxidation of *p*-nitroso phenol to *p*-nitro derivative in presence of oxygen see: *The Chemistry of Phenols*; Rappoport, Z., Ed.; Wiley: Chichester, UK, 2003; Chapter 9, p 639, and references therein.

(27) A comparable selectivity was observed in the nitrosation of secondary amides by nitrosonium⊂calixarene camplexes (see ref 12c and Zyryanov, G. V.; Rudkevich, D. M. *Org. Lett.* **2003**, *5*, 1253).

(28) For other examples of supramolecular control of a reaction outcome, see: (a) Maia, A.; Landini, D.; Penso, M.; Brandt, K.; Siwy, M.; Schroeder, G.; Gierczyk, B. *New J. Chem.* **2001**, *25*, 1078. (b) Chen, J.; Rebek, J., Jr. *Org. Lett.* **2002**, *4*, 327. (c) Iwasawa, T.; Mann, E.; Rebek, J., Jr. *J. Am. Chem. Soc.* **2006**, *128*, 9308.