Synthesis of a Calix[4]arene Derivative for Isolation of a Stable Cation Radical Salt for Use as a Colorimetric Sensor of Nitric Oxide

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The calixarene derivatives are extensively utilized as molecular platforms for the design and synthesis of novel materials in supramolecular chemistry.[1] The cofacial arrangement of aromatic moieties in various *t*-buytlcalix[4]arene conformers (especially in the 1,3-alternate conformer) creates an electron-rich cavity that allows the cationic nitrosonium ion (NO^+) to penetrate deep inside the cavity of these molecular hosts.[2] To make use of the calixarene cavity for binding electron-rich guests such as nitric oxide (NO), a molecule of vital biological importance,[3] one would require an appropriate electronic modification of the aryl groups of calixarenes to yield an electron-deficient cavity.[4] The cation radicals of various conformers of parent calixarene ethers, formed by 1-electron oxidation at low temperatures (-78 °C), contain the desired electron-deficient cavities that may be well suited for binding electron-rich guests; however, these cation radicals are highly unstable and decompose even at -78 °C upon prolonged storage (>10 min).[5] It is evident that one requires a modified calixarene derivative that can yield a stable cation radical without altering the shape and size of the cavity. Rathore et al.[6] have recently noted that the incorporation of 2,5-dimethoxytolyl as an electron donor on the vertexes of the hexaphenylbenzene core allowed the isolation of a highly robust hexacation radical salt from *hexakis*(4-methyl-2,5-dimethoxybiphenyl)benzene. It was envisioned that the synthesis of a modified calixarene derivative in which the *tert*-butyl groups in parent calixarene are replaced by the same electron-donor groups (see structure **1**) may allow the isolation of a stable cation radical salt. Moreover, it is expected that the hole will be shared among the 2,5-dimethoxy-tolyl and the aryl groups of the calixarene core in its cation radical salt **1⁺•** (See Scheme 1).

Scheme 1
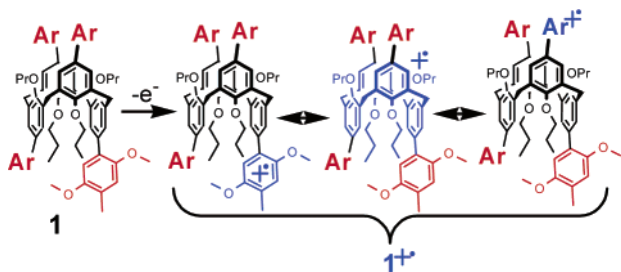
Accordingly, herein we now report the preparation of a (1,3-alternate) calix[4]arene ether derivative (**1**) that allows the preparation of a stable cation radical either via a chemical or an equivalent electrochemical oxidation, and the resulting cation radical (with its intact electron-deficient cavity) shows dramatic color changes upon exposure to gaseous nitric oxide (NO). Moreover, the remarkable efficiency of this modified calixarene host toward NO binding is demonstrated with the aid of optical spectroscopy, by

Scheme 2. Synthesis of Electroactive Calixarene Derivatives[a]
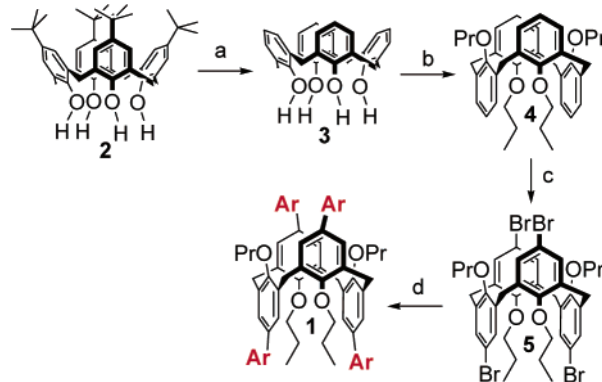
[a] Conditions: (a) phenol, $AlCL_3$, toluene, reflux, 71%; (b) *n*-propyltosylate, Cs_2CO_3, DMF, 80 °C, 82%; (c) NBS, methanol, 67%; (d) 2,5-dimethoxytolylmagnesium bromide (4.2 equiv), $(PPh_3)PdCl_2$, THF, reflux, 75%.

isolation of a crystalline complex [**1**, NO]⁺, and by its characterization by X-ray crystallography as follows.

The electroactive calixarene derivative **1** was obtained by a four-step reaction sequence from the readily available *tert*-butylcalix-[4]arene (**2**) as summarized in Scheme 2. The key step in the synthesis involved a Kumada-type coupling of tetrabromo-calix-arene **5** with 2,5-dimethyoxytolylmagnesium bromide in the presence a catalytic amount of bis-triphenylphosphinepalladium dichloride in THF in excellent yield (see Scheme 2). The experimental details and the characterization data for **1** are described in Supporting Information. Moreover, the structure determination of tetraarylcalixarene ether **1** by X-ray crystallography confirmed that the replacement of *tert*-butyl groups with 2,5-dimethoxytolyl (Ar) groups did not alter the shape or the size of the cavity in any significant way (vide infra).

With the tetraarylcalixarene **1** at hand, we first evaluated its electron-donor strength and the initial indication of the cation radical stability by cyclic voltammetry. Thus, an electrooxidation of **1** in dichloromethane solution (containing *n*-tetrabutylammonium hexafluorophosphate as a supporting electrolyte) at a scan rate of 200 mV s⁻¹ showed two reversible oxidation waves together with an irreversible wave in its cyclic voltammogram (see Figures S1 and S2 in Supporting Information). A quantitative evaluation of the CV peak currents with added ferrocene (as an internal standard) revealed that the first oxidation potential ($E_{ox1} = 1.07$ V vs SCE) was significantly lower than the second ($E_{ox2} = 1.27$ V) and the higher oxidation events ($E_{ox3} > 1.55$ V). Such an observation of the splitting of the oxidation waves arising from four **Ar** groups[7] in the CV of **1** suggests that the oxidation of one of the **Ar** groups affects the removal of further electrons from the other three **Ar** groups and thus provides the first indication that the aryl groups are electronically coupled to each other via the calixarene framework (see Scheme 1).[7]

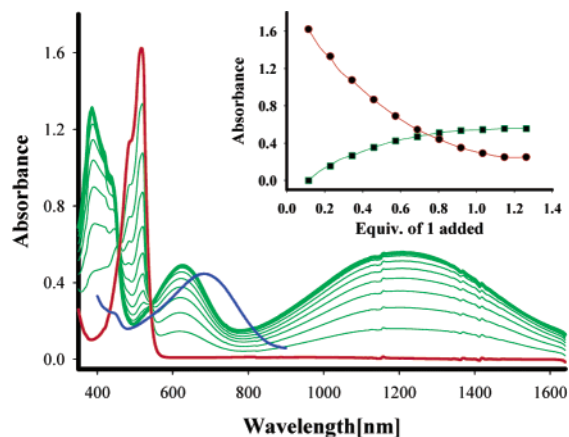**Figure 1.** Spectral changes upon the reduction of $MA^{+\bullet}$ $SbCl_6^-$ (red) by an incremental addition of **1** to its cation radical $1^{+\bullet}$ (green) in CH_2Cl_2 at 22 °C. Inset: plot of depletion of $MA^{+\bullet}$ (red line, 516 nm) and formation of $1^{+\bullet}$ (black squares, 1200 nm) against the number of equivalents of **1** added. Blue spectrum is obtained upon exposure of the green $1^{+\bullet}$ to gaseous NO.

The electrochemical reversibility of **1** prompted us to carry out its oxidation to the corresponding cation radical using the stable aromatic cation radical salts $MA^{+\bullet}$ $SbCl_6^-$ as an oxidant (E_{red} = 1.11 V vs SCE).[8] Thus, Figure 1 shows the spectral changes attendant upon the reduction of 2.2×10^{-4} M $MA^{+\bullet}$ [λ_{max} (log ϵ) = 516 nm (3.86)] by incremental additions of 4.1×10^{-3} M **1** at 22 °C in dichloromethane. The presence of well-defined isosbestic points at λ_{max} = 465 and 542 nm in Figure 1 are indicative of the uncluttered character of the electron transfer. Furthermore, a plot of the depletion of $MA^{+\bullet}$ (i.e., decrease in the absorbance at 516 nm) and formation of $1^{+\bullet}$ (i.e., increase in the absorbance at 1200 nm) against the increments of added **1** (inset, Figure 1) established that $MA^{+\bullet}$ was completely consumed after the addition of 1 equiv of **1**; and the resulting absorption spectrum of $1^{+\bullet}$ [λ_{max} (log ϵ) = 375 (3.78), 620, 1200 nm] remained unchanged upon further addition of neutral **1** (i.e., eq 1).

$$MA^{+\bullet} + 1 \rightarrow 1^{+\bullet} + MA \qquad (1)$$

The green-colored $1^{+\bullet}$ obtained in eq 1 is stable at 22 °C, and the neutral **1** can be recovered quantitatively upon reduction with zinc dust. Moreover, the pure calixarene cation radical ($1^{+\bullet}$ $SbCl_6^-$) can also be prepared using triethyloxonium hexachloroantimonate as the one-electron oxidant (see Supporting Information).

When the solution of the $1^{+\bullet}$ was exposed to gaseous nitric oxide (NO) at 22 °C, the bright green color was immediately replaced by a dark blue coloration, and the spectrum of the resulting solution showed a broad absorption band at λ_{max} = 690 nm (ϵ_{690} = 3000 M^{-1} cm^{-1}) (see the blue spectrum in Figure 1).

Infrared spectral analysis of the blue solution confirmed that the N—O stretching band at 1906 cm^{-1} in $[1/NO]^+$ is characteristically close to that observed for free nitric oxide (1876 cm^{-1}), and the high affinity of $1^{+\bullet}$ toward NO ($K_{NO} > 10^8$ M^{-1})[9] allowed the ready isolation of single crystals of blue $[1/NO]^+$ from a mixture of dichloromethane and hexanes at 0 °C. X-ray crystallography at −150 °C established the molecular structure of $[1/NO]^+$ $SbCl_6^-$ to consist of a single molecule of NO trapped inside the calixarene core.

The effective sharing of the cationic hole among the electroactive dimethoxytolyl groups and calixarene core (see Scheme 1) allows a single molecule of NO to be completely encapsulated deep inside the calixarene cavity and is distributed equally between chemically equivalent distal aromatic pairs that form the cylindrical cavity of
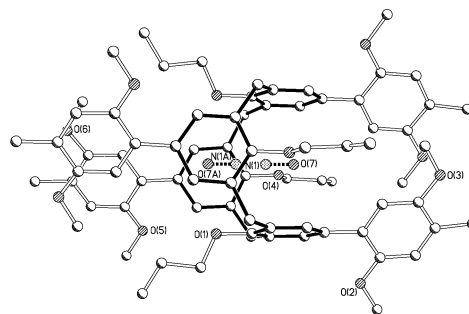

Figure 2. X-ray crystal structure of NO-bound 1,3-alternate conformer of tetraarylcalix[4]arene ether $[1, NO]^+$. Hydrogens and hexachloroantimonate anion ($SbCl_6^-$) are omitted for the sake of clarity.

the calixarene core (see Figure 2). The noncovalent interaction of the cationic calixarene cavity positions NO between the cofacial aromatic rings (of the calixarene core) at a distance of 2.4 Å that is substantially shorter than the van der Waals contact (3.2 Å). Furthermore, the similarity of the bond lengths in dimethoxytolyl groups both in neutral **1** and its cationic NO-bound complex suggests that the charge is largely localized on the calixarene core in $[1/NO]^+$.

In summary, we have designed and synthesized a modified calixarene derivative that allows, for the first time, the isolation of a stable cation radical that binds a single molecule of nitric oxide deep within its cavity with remarkable efficiency ($K_{NO} > 10^8$ M^{-1}). Moreover, the ready accessibility of the electron-rich calixarene donor as well as its (electron-poor) cation radical will allow us to explore their use for developing efficient sensing devices for nitric oxide based on the accompanying color changes as well as using electrochemical techniques.[10] These works are being pursued actively.

Supporting Information Available: Preparation and spectral data for **1** and various intermediates, $1^{+\bullet}$, cyclic voltammograms, and X-ray data for **1** and $[1/NO]^+$ (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) Note that the through-space separation between electron-rich dimethoxy-tolyl groups is >5 Å, and thus electronic coupling amongst them is feasible only through the calixarene core.
(8) For the preparation of $MA^{+\bullet}$ $SbCl_6^-$ (9,10-dimethoxyocta-hydro-1,4:5,8-dimethanoanthracene cation radical), see: Rathore, R.; Burns, C. L. *Org. Synth.* **2003** (procedure being checked).
(9) Binding constant was too large to be determined directly and thus was estimated using Venus fly trap ($K_{ass} = 3 \times 10^6$ M^{-1} for NO binding) according to a competition method; see ref 2 for details.
(10) For the other methods of nitric oxide sensing, compare: Hilderbrand, S. A.; Lim, H. H.; Lippard, S. J. *J. Am. Chem. Soc.* **2004**, *126*, 4972 and references therein.

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