Guest Penetration Deep within the Cavity of Calix[4]arene Hosts: The Tight Binding of Nitric Oxide to Distal (Cofacial) Aromatic Groups**

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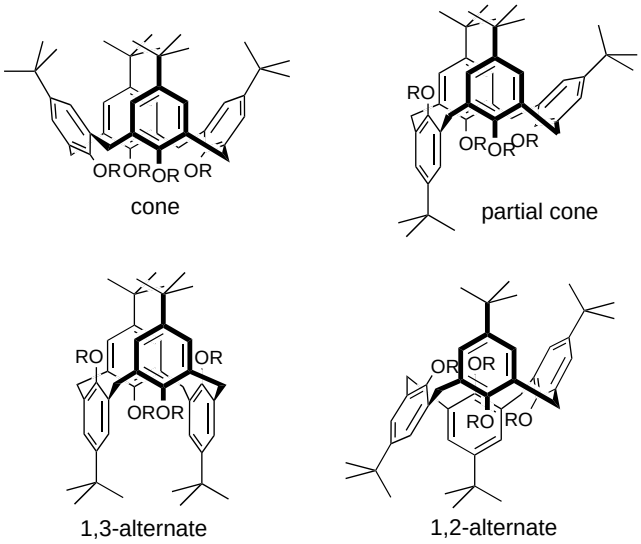
Interest in the design and synthesis of modified calixarenes derives from their importance as molecular platforms or building blocks in supramolecular chemistry.[1–3] The most relevant structural feature of calixarene hosts is the presence of a macrocyclic cavity that holds potential for binding various (guest) substrates. However, calix[4]arenes complexes such as those with various alkali as well as transition metal cations generally utilize the "hard" oxygen atoms on the rim rather than the "soft" π-basic cavity formed by the four-electron-rich aryl groups.[4, 5] Even cationic π-acceptors such as silver(I) ions do not penetrate into the interior of the cavities of the calix[4]arenes, but position themselves on the outside of the wider rim.[6]

Calix[4]arenes and their tetramethyl ether derivatives are conformationally mobile molecules with four rapidly interconverting conformers that contain cavities of variable size and shape.[7, 8] Importantly, each conformer contains at least one pair of juxtaposed aromatic rings (Scheme 1). We find a cofacial arrangement of aromatic groups results in a cleft in the stilbenoid hydrocarbon ligand "Venus flytrap" that efficiently traps nitric oxide (NO)—a molecule of significant biological interest owing to its importance as an intercellular messenger[9] in a variety of physiological processes.[10] Accordingly, we conjectured whether the void created by cofacial aromatic groups in various calixarene conformers would allow the actual penetration of nitric oxide into the interior of the calixarene cavities. Moreover, such an association of a guest (namely NO) with calixarene may also modulate its conformational mobility as well as the distribution of the conformers.



Scheme 1. The four characteristic confermers of lower-rim-functionalized *p-tert*-butylcalix[4]arene.

We now report that the conformationally mobile calix[4]arene methyl ether derivative[7] (**1**-OMe; Scheme 1, R = Me) readily captures nitric oxide (by complete encapsulation) deep inside its cavity, which results in all four conformations becoming immobile in solution (on the NMR time scale). Crystallization yields purple crystals of NO-bound calixarene as a single (1,3-alternate) conformer, as confirmed by X-ray crystallography and NMR spectroscopy. For comparison, we also examined the rigid conformers of the calix[4]arene propyl ether derivative[11] (**2**-OPr; Scheme 1, R = propyl) to probe the binding properties and dynamics of differently structured calixarene cavities toward this guest.

The activation of calixarene **1**-OMe by oxidation in dichloromethane produces a bright yellow solution,[12] which upon exposure to gaseous nitric oxide takes on a dark purple color [Eq. (1)].[13] Infrared spectral analysis of the purple solution indicates the quantitative entrapment of NO, as gauged by the characteristic IR absorption at 1958 cm^{-1} corresponding to a single N-O stretching frequency.[14]

$$\mathbf{1}\text{-OMe} \xrightarrow[(-e^-)]{+NO} \underset{\text{(purple)}}{[\mathbf{1}\text{-OMe, NO}]^+} \quad (1)$$

Importantly, the same purple solution is also obtained by exposure of a solution of calixarene **1**-OMe in dichloromethane to oxidized nitric oxide (NO^+)[15] [Eq. (2)].

$$NO \xrightarrow[(-e^-)]{+\mathbf{1}\text{-OMe}} [\mathbf{1}\text{-OMe, NO}]^+ \quad (2)$$

Dark purple solutions of NO-bound calixarene are unusually stable and show no sign of decomposition even after standing at room temperature for several months. Such a remarkable stability is further confirmed by an exceptionally high binding constant of $K_{ass} > 5 \times 10^8\,M^{-1}$ for the association of nitric oxide with **1**-OMe in Equations (1) and (2).[16]

To determine the structure of the NO-bound calixarene methyl ether, we crystallized [**1**-OMe, NO]$^+$ from a mixture of dichloromethane and hexane at about 0 °C. Interestingly, the well-formed crop of highly colored single crystals (in 94% yield) show similar morphology despite the fact that calixarene **1**-OMe contains four conformers in solution. Indeed, the X-ray crystallographic analysis of several single crystals from different batches uniformly exhibit identical cell parameters, which are all identified as those of the 1,3-alternate conformer of [**1**-OMe, NO]$SbCl_6$.[17] Figure 1 shows that a single molecule of NO is completely entombed deep inside the calixarene cavity, and is only visible if one of the methoxy groups is omitted in the space-filling representation. The cylindrical cavity of the 1,3-alternate conformer is defined by two distal (cofacial) pairs of aromatic groups oriented orthogonally

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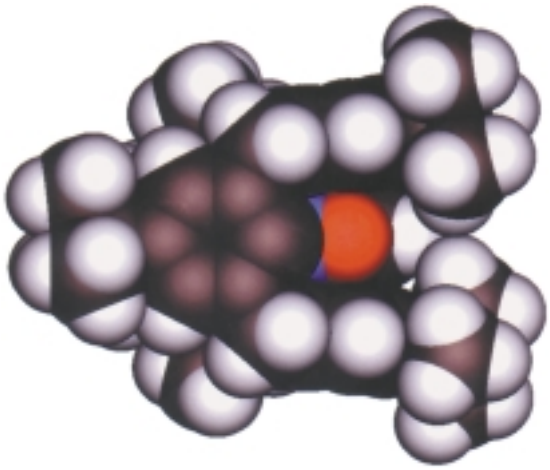

Figure 1. Space-filling representation of [**1**-OMe, NO]$^+$ with one of the methoxy groups omitted to reveal the deeply nestled NO.

along the cavity axis. The NO molecule is distributed equally between these chemically equivalent aromatic pairs as shown in Figure 2.[18] Moreover, we believe that the disordered guest

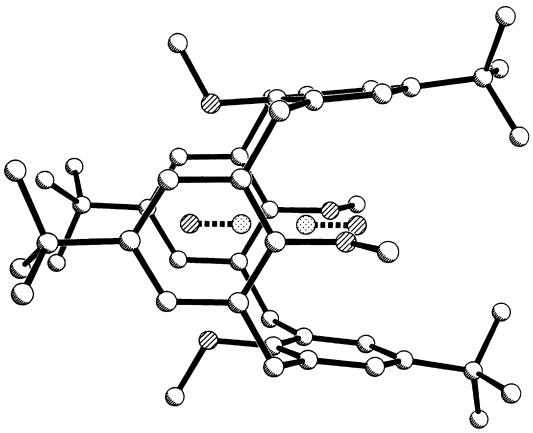

Figure 2. Molecular structure of [**1**-OMe, NO]$SbCl_6$ showing (disordered) nitric oxide distributed equally between the two orthogonally oriented cofacial pairs of aromatic rings that form the cylindrical cavity characteristic of the 1,3-alternate conformer. (Hydrogen atoms and the hexachloroantimonate anion are omitted for clarity.)

(NO) in the 1,3-alternate conformer interchanges its position rapidly between two symmetrically equivalent sites within the calixarene cavity—as evidenced by the simple ^{1}H NMR spectrum (see below), which suggests that all the aryl groups are chemically equivalent in solution even at very low temperatures. It is noteworthy that this novel molecular structure of a NO-bound calix[4]arene constitutes a unique example of a guest (namely NO) that penetrates deep inside the cavity.[19] The strong noncovalent (charge-transfer) interactions of nitric oxide with the "soft" π-core of calixarene position it in between the cofacial aromatic rings at a distance (2.4 Å) that is substantially shorter than the van der Waals contact (3.2 Å).

It is noteworthy that the dark purple crystals of the 1,3-alternate conformer of [**1**-OMe, NO]$^+$ are stable indefinitely in the solid state at room temperature. We monitored the ^{1}H NMR spectra of the purple crystals dissolved in CD_2Cl_2 over time to determine its stability in solution. The solution of the 1,3-alternate [**1**-OMe, NO]$^+$ ion is stable at least for 30 min and shows four characteristic singlets in the ^{1}H NMR spectrum (Figure 3a) consistent with its structure.[20] However, during the course of 24 h it slowly converts into a

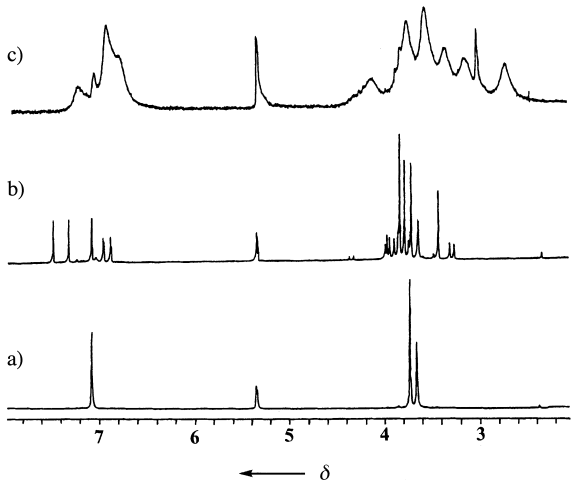

Figure 3. Partial ^{1}H NMR spectra of isolated 1,3-alternate conformer of [**1**-OMe, NO]$^+$ (a), conformational mixture of [**1**-OMe, NO]$^+$ at equilibrium (b), and uncomplexed **1**-OMe (c) in CD_2Cl_2 at 25 °C. (Note that the signals for the *tert*-butyl groups are omitted from the various spectra for clarity.)

mixture of conformers (Figure 3b), which is identical to the mixture of conformers obtained by merely dissolving **1**-OMe and $NOSbCl_6$ in CD_2Cl_2. The observation of sharp peaks in the NMR spectrum corresponding to four conformers[21] indicates that the association of NO with **1**-OMe inhibits any conformational mobility on the NMR time scale. In contrast, uncomplexed calixarene **1**-OMe shows broadened NMR signals (Figure 3c) owing to the rapid interconversion of its four conformations (at room temperature), and the resolved signals for the various conformations are only observed at a lower temperature (−30 °C).[8] The striking preference in the crystallization of the 1,3-alternate (least-stable)[7, 8] conformer of [**1**-OMe, NO]$^+$ points to a crystallization-induced drainage of the slow equilibrium amongst the four conformations in solution.

In an attempt to obtain pure uncomplexed 1,3-alternate conformer of **1**-OMe in solution, crystalline [**1**-OMe, NO]$^+$ was dissolved in CD_2Cl_2 and mixed with a prechilled solution of chloride anions (as bis(triphenylphosphoranylidene)ammonium chloride) at −78 °C. As a result, the solution bleached instantaneously as a result of the formation of uncomplexed **1**-OMe and NOCl [Eq. (3)].[22]

$$[\mathbf{1}\text{-OMe, NO}]^+ + Cl^- \xrightarrow{\text{V. fast}} \mathbf{1}\text{-OMe} + NOCl \qquad (3)$$

The ^{1}H NMR spectrum of the resulting solution, recorded immediately at −78 °C, shows the presence of a characteristic mixture of conformers of uncomplexed **1**-OMe. This rapid conversion of one conformer of **1**-OMe to the mixture of conformations even at low temperatures is to be contrasted

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with the slow isomerization of [**1**-OMe, NO]$^+$ at room temperature (see above).[23]

To gauge the relative binding abilities of various conformers of calix[4]arene separately towards NO, we examine the rigid conformers of the propyl ether derivative (**2**-OPr).[12] First, we note that all the conformers of **2**-OPr show blue to purple coloration upon binding to NO,[24] and the solutions are stable for months if protected from moisture. The high stability of [**2**-OPr, NO]$^+$ allows the ready isolation of single crystals of NO-bound 1,3-alternate, cone, and partial cone conformers by slow evaporation of the highly colored solutions in dichloromethane at room temperature. The X-ray structure analysis shown in Figure 4 confirms that in each conformer one pair of cofacial aromatic groups is sufficient for complete entrapment of NO deep inside the calixarene cavity. The NO-bound 1,3-alternate conformers from **1**-OMe and **2**-OPr are essentially isostructural. As yet we are unable to obtain single crystals from the 1,2-alternate conformer that are suitable for X-ray crystallography.[25]

The similarities in the structures of the various NO-bound calixarene ethers in Figures 1 and 4 are further reflected in their binding abilities towards NO.[25] Thus, we attempted to estimate the association constants (K_{ass}) for the binding of NO with various conformers of **2**-OPr, using the ratios of integral intensities of ^{1}H NMR signals of the complexes and the free calixarenes which appear separately.[26] However, in each case the integral intensity of the complex matches the amount of added NO$^+$ salt, which implies that K_{ass} is too large to be measured by NMR spectroscopy. However, estimates of $K_{ass} > 5 \times 10^8\ M^{-1}$ are obtained for all conformers by a competition method using the Venus flytrap.[27] Such large binding constants found with all calixarene ethers are unprecedented, and they are readily explained by a complete incarceration of NO into the interior of the calixarene cavities by utilizing a pair of cofacial (parallel) aromatic groups.[28] We are presently exploring ways to exploit the remarkable binding abilities of calixarenes for the construction of novel molecular sensors for NO as well as other small molecules.

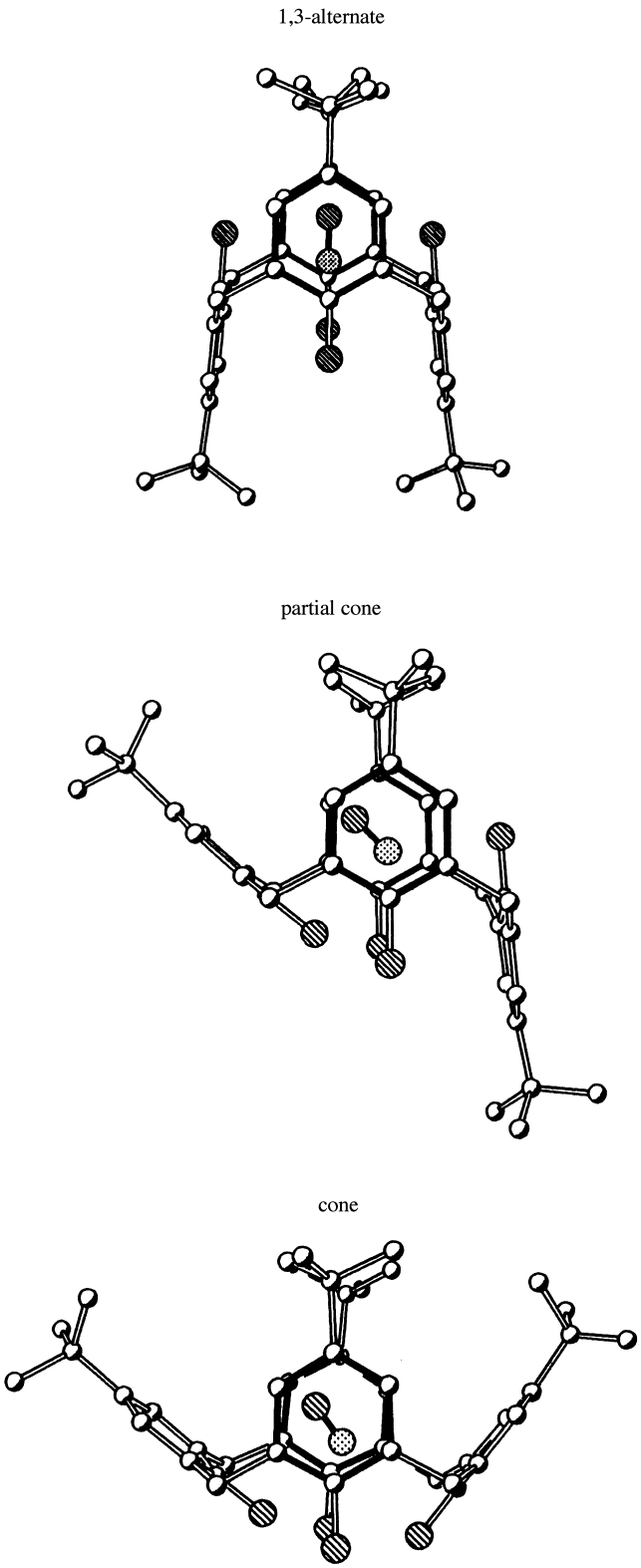

Figure 4. X-ray structures of cone, partial cone, and 1,3-alternate conformers of [**2**-OPr, NO]$^+$ showing nitric oxide perfectly sandwiched between a pair of cofacial aromatic groups in each structure. (Hydrogen atoms and propyl groups are removed for clarity.)

Experimental Section

The calix[4]arene ethers were prepared according to literature procedures[7, 11] and crystallized from a mixture of methanol and dichloromethane. The calixarene ethers were dried in vacuo overnight prior to all complexation studies.

X-ray crystallography. The intensity data were collected at $-150\,^\circ$C on a Siemens SMART diffractometer equipped with a CCD detector using $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å). The structures were solved by direct methods[29] and refined by full matrix least-squares procedures. Crystal Data for [**1**-OMe, NO]$SbCl_6$: $[C_{48}H_{64}O_4, NO] \cdot SbCl_6 \cdot CH_2Cl_2$, $M_r =$ 1154.38, tetragonal $P4/n$, $a = 14.654(2)$, $b = 14.654(2)$, $c = 12.583(3)$ Å, $\rho_{calcd} = 1.419\ Mg\,m^{-3}$, $V = 2702.0(8)$ Å^3, $Z = 2$. The total number of reflections measured was 33028, of which 5983 reflections were symmetrically nonequivalent. Final residuals were $R1 = 0.0333$ and $wR2 = 0.0656$ for 5983 reflections with $I > 2\sigma(I)$. Crystal data for cone conformer of [**2**-OPr, NO]$SbCl_6$: $[C_{56}H_{80}O_4, NO] \cdot SbCl_6 \cdot CH_2Cl_2 \cdot 0.5\,C_7H_8$, $M_r = 1312.65$, monoclinic, $P2_1$, $a = 12.6304(5)$, $b = 24.151(1)$, $c = 20.4071(9)$ Å, $\beta =$ 94.408(1)°, $\rho_{calcd} = 1.339\ Mg\,m^{-3}$, $V = 6510.6(5)$ Å^3, $Z = 4$. The total number of reflections measured was 62475, of which 38612 reflections were symmetrically nonequivalent. Final residuals were $R1 = 0.0886$ and $wR2 =$ 0.2370 for 38612 reflections with $I > 2\sigma(I)$. Crystal data for partial cone conformer of [**2**-OPr, NO]$SbCl_6$: $[C_{56}H_{80}O_4, NO] \cdot SbCl_6 \cdot C_7H_8$, $M_r =$ 1273.79, triclinic, $P\bar{1}$, $a = 12.8177(5)$, $b = 14.4156(5)$, $c = 19.1344(7)$ Å, $\alpha =$ 75.745(1)°, $\beta = 70.585(1)°$, $\gamma = 75.773(1)°$, $\rho_{calcd} = 1.331\ Mg\,m^{-3}$, $V =$ 3179.5(2) Å^3, $Z = 2$. The total number of reflections measured was 45348, of which 26946 reflections were symmetrically nonequivalent. Final residuals were $R1 = 0.0508$ and $wR2 = 0.1322$ for 26946 reflections with

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$I > 2\sigma(I)$. Crystal Data for 1,3-alternate conformer of [**2**-OPr, NO]$SbCl_6$: $[C_{56}H_{80}O_4, NO] \cdot SbCl_6$, $M_r = 1181.66$, monoclinic, $P2_1/n$, $a = 12.573(2)$, $b = 33.922(5)$, $c = 14.484(2)$ Å, $\beta = 100.201(4)^o$, $\rho_{calcd} = 1.291\ Mg\,m^{-3}$, $V = 6079.9(15)$ Å^3, $Z = 4$. The total number of reflections measured was 45959, of which 12461 reflections were symmetrically nonequivalent. Final residuals were $R1 = 0.0566$ and $wR2 = 0.1581$ for 12461 reflections with $I > 2\sigma(I)$. (Note that this structure was solved at room temperature and at $-30\,^\circ C$.) Crystal data for [2,6-dimethyl-4-tert-butylanisole, NO]$SbCl_6$: $[C_{13}H_{20}O, NO] \cdot SbCl_6$, $M_r = 556.75$, orthorhombic, $Pca2_1$, $a = 15.6673(9)$, $b = 15.3129(9)$, $c = 17.3455(10)$ Å, $\rho = 1.777\ Mg\,m^{-3}$, $V = 4161.4(4)$ Å^3, $Z = 8$. The total number of reflections measured was 58295, of which 18065 reflections were symmetrically nonequivalent. Final residuals were $R1 = 0.0277$ and $wR2 = 0.0628$ for 18065 reflections with $I > 2\sigma(I)$. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-139590 – 139595. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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[12] The oxidation of calix[4]arene methyl ether (**1**-OMe) yields the yellow-green cation radical ($\lambda_{max} = 440$ nm and a very broad band extending beyond 1600 nm). The one-electron oxidation can also be carried out electrochemically at $E^0_{ox} = 1.4$ V versus the saturated calomel electrode (SCE) in anhydrous dichloromethane (containing tetra-*n*-butylammonium hexafluorophosphate as the supporting electrolyte) or by electron transfer with either the stable cation radical of 1,1,4,4,7,7,10,10-octamethyloctahydronaphthacene (R. Rathore, P. Le Maguerès, S. V. Lindeman, J. K. Kochi, *Angew. Chem.* **2000**, *112*, 818; *Angew. Chem. Int. Ed.* **2000**, *39*, 809) or a mixture of trifluoroacetic acid and dichlorodicyanobenzoquinone in dichloromethane (R. Rathore, J. K. Kochi, *Acta Chem. Scand*. **1998**, *52*, 114).

[13] UV/Vis spectral analysis confirms that the color arises from a broad UV/Vis absorption band at $\lambda_{max} = 546$ nm, $\varepsilon_{max} = 7600\ M^{-1}\,cm^{-1}$.

[14] Free NO absorbs at $\tilde{\nu}_{NO} = 1875\ cm^{-1}$ (W. G. Fateley, H. A. Bent, B. Crawford, Jr., *J. Chem. Phys.* **1959**, *31*, 204). For the IR data for other NO complexes, see E. K. Kim, J. K. Kochi in ref. [28].

[15] The nitrosonium (NO^+) cation was used as the hexachloroantimonate ($SbCl_6^-$) salt.

[16] Such a high association constant for NO is unprecedented and exceeds the value previously reported for Venus flytrap by at least two orders of magnitudes.[10]

[17] Note that no fewer than 10 crops from three crystallizations at different temperatures invariably yielded crystals with identical cell parameters (see Experimental Section)

[18] The uncomplexed 1,3-alternate conformer of **1**-OMe (belonging to a point symmetry S_4) occupies the special position of symmetry -4 (that is, an inversion fourfold axis) in the crystals of [**1**-OMe, NO]$^+$. Such symmetry requires the NO to be disordered and equally distributed over two positions along the twofold axis (a subelement of -4 symmetry). Unfortunately, X-ray crystallographic studies do not distinguish between dynamic and statistical disorder.

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[20] The four singlets in the ^1H NMR spectrum of 1,3-alternate [**1**-OMe, NO]$^+$ in Figure 3a appear at $\delta = 1.33$ (36H), 3.64 (8H), 3.72 (12H), and 7.08 (8H), and are deshielded relative to the uncomplexed **1**-OMe.[7]

[21] The conformational distribution of [**1**-OMe, NO]$^+$ in solution at equilibrium is (roughly) estimated to be 70:15:10:5 for partial cone, cone, 1,3-alternate, and 1,2-alternate, respectively. This conformer distribution is slightly different from that of the uncomplexed **1**-OMe in CD_2Cl_2.[7, 8]

[22] NOCl was identified by comparison of the UV/Vis spectra with an authentic sample, see D. W. A. Scharp, J. Thornley, *J. Chem. Soc.* **1963**, 3557.

[23] a) The slow equilibration of 1,3-alternate conformer of [**1**-OMe, NO]$^+$ may be accounted by the fact that it cannot undergo isomerization while it is complexed to NO. We believe that the rapid shuttling of NO within the calixarene cavity may lead to occasional NO loss (despite the high binding constants); and the resulting uncomplexed **1**-OMe undergoes rapid isomerization to the four characteristic conformers (see above) followed by complexation with NO.b) Unfortunately, we are as yet unable to cool the solution to temperatures low enough to observe a stabilized (uncomplexed) 1,3-alternate conformer of **1**-OMe.

[24] The UV/Vis spectral data for the various conformations of [**2**-OPr, NO]$^+$ in dichloromethane are as follows: cone: $\lambda_{max} = 572$ nm, $\varepsilon_{max} = 8800\ M^{-1}\,cm^{-1}$; partial cone: $\lambda_{max} = 556$ nm, $\varepsilon_{max} = 7700\ M^{-1}\,cm^{-1}$; 1,3-alternate: $\lambda_{max} = 569$ nm, $\varepsilon_{max} = 5600\ M^{-1}\,cm^{-1}$; 1,2-alternate: $\lambda_{max} = 540$ nm, $\varepsilon_{max} = 1900\ M^{-1}\,cm^{-1}$ with a shoulder at 420 nm.[25]

[25] The UV/Vis absorption band of the 1,2-alternate conformer shows a prominent shoulder at 420 nm as well as a considerably reduced molar absortivity,[24] which suggests an incomplete overlap of nitric oxide with the aromatic groups as a result of the unique structure of this conformer. see: R. Rathore, S. V. Lindeman, J. K. Kochi in ref. [28].

[26] ^1H NMR data for various conformers of [**2**-OPr, NO]$^+$ in $CDCl_3$ at 25 °C are as follows: 1,3-alternate: $\delta = 1.03$ (t, 12H), 1.30 (s, 36H), 1.88 (m, 8H), 3.75 (t, 8H), 3.63 (s, 8H), 7.03 (s, 8H); cone: $\delta = 1.08$ (t, 12H), 1.13 (s, 36H), 1.99 (m, 8H), 3.49 (d, $J = 12.9$ Hz, 4H), 4.02 (t, 8H), 4.42 (d, $J = 12.9$ Hz, 4H), 7.00 (s, 8H); partial cone: $\delta = 0.7 - 1.95$

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(m, 20H), 1.11 (s, 18H), 1.40 (s, 9H), 1.49 (s, 9H), 3.41 (d, $J = 12.9$ Hz, 4H), 3.75 (m, 6H), 3.94 (m, 2H), 4.06 (d, $J = 13.0$ Hz, 4H), 6.80 (d, 2H), 6.92 (d, 2H), 7.35 (s, 2H), 7.61 (s, 2H); 1,2-alternate: $\delta = 0.77$ (t, 12H), 0.90 (m, 4H), 1.44 (m, 4H), 1.48 (s, 36H), 2.91 (d, 2H), 3.55 (m, 4H), 3.62 (m, 4H), 3.63 (s, 4H), 3.97 (d, 2H), 7.12 (d, 4H), 7.22 (d, 2H).

[27] The binding constants are estimated using the Venus flytrap ($K_{ass} = 3 \times 10^6\,\text{M}^{-1}$ for NO incarceration) according to a competition method described earlier, see E. Bosch, J. K. Kochi, *J. Org. Chem.* **1995**, *60*, 3172.

[28] In contrast, the model 2,6-dimethyl-4-*tert*-butylanisole (DMBA) results in a pale red-brown solution upon mixing with $NOSbCl_6$ ($K_{ass} \sim 700\,\text{M}^{-1}$) in dichloromethane at 25 °C. X-ray structure analysis of a single crystal of DMBA complexed with NO^+ grown from a mixture of dichloromethane and hexane at −30 °C shows an approximately perpendicular orientation of NO poised centrally over the aromatic ring (see Experimental Section). This structure is similar to those observed previously with other single aromatic donors such as hexamethylbenzene (R. Rathore, S. V. Lindeman, J. K. Kochi, *J. Am. Chem. Soc.* **1997**, *119*, 9393) and mesitylene (E. K. Kim, J. K. Kochi, *J. Am. Chem. Soc.* **1991**, *113*, 4962).

[29] G. M. Sheldrick, SHELSX-86. Program for Structure Solution, University of Göttingen: Germany (**1986**).

A Transition State for the Enantioselective Deprotonation of *N*-Boc-Pyrrolidine with Isopropyllithium/(−)-Sparteine**

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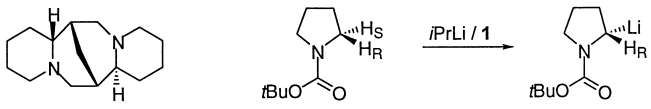
Over the course of the past decade, pioneering studies by the groups of Hoppe[1] and Beak[2] have demonstrated that the 1:1 complex of a *sec*-alkyllithium (such as *sec*-BuLi or *i*PrLi) and (−)-sparteine (**1**) is a remarkably efficient reagent for the highly enantioselective deprotonation that produce configurationally stable dipole-stabilized organolithium species.[3] A particularly simple example of such an asymmetric deprotonation is provided by the lithiation of *N*-Boc-pyrrolidine (**2**; Boc = *tert*-butyloxycarbonyl) with *i*PrLi/(−)-sparteine (Scheme 1). Beak et al. have shown that this kinetically controlled process proceeds with a remarkably high selectivity ($95 \pm 5\,\%$)[2c] for abstraction of the *pro-S* hydrogen atom at C(2).[2, 3] Moreover, **1** appears to be the ligand of choice for such a deprotonation: A variety of structurally diverse chiral



Scheme 1. Kinetically controlled deprotonation of *N*-Boc-pyrrolidine.

diamines have been screened as potential ligands for the asymmetric deprotonation of **2** but none was found to be nearly as effective as is **1**.[2d]

In light of the current interest in development of a transition state model that accounts for the ability of *sec*-alkyllithium/(−)-sparteine to effect highly enantioselective deprotonation,[3–5] it was of interest to investigate whether modern ab initio molecular orbital calculations could adequately describe the outcome of the asymmetric deprotonation of **2**. In this connection, we have recently reported a computational study of the conformational isomers of **1** and of the transition states for their interconversion.[6] We also have examined the complexes of **1** with both LiH and with *n*PrLi; in each of these cases, **1** behaves as a bidentate ligand and adopts a conformation that lies just above the lowest energy conformer for the uncomplexed ligand.[6] The structure of the LiH/(−)-sparteine complex is shown in Figure 1.

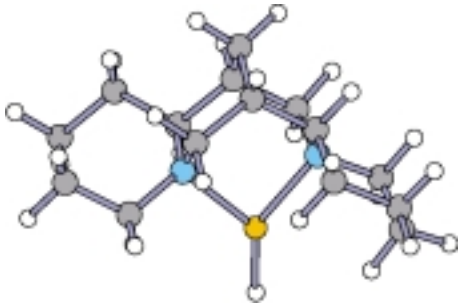


Figure 1. The LiH complex of (−)-sparteine; nitrogen atoms are blue, lithium is orange.

On the reasonable assumption that the deprotonation reaction depicted in Scheme 1 involves precomplexation of the base, ligand, and substrate,[3, 7] the reactive species would have an isopropyl group in place of the hydrogen atom shown in Figure 1 and the carbonyl group of **2** would presumably serve as a fourth ligand, which gives a near-tetrahedral arrangement around the lithium atom. Thus, with respect to the view portrayed in Figure 1, the *i*Pr group may be either forward or behind the plane and **2** takes the other position. Similarly, the pyrrolidine ring of **2** may be either to the right or the left of the lithium atom and the *tert*-butoxy group occupies the other position. Given these preliminaries, there are four potential structures to be examined.

Because of the very large size of the complexes ($C_{27}H_{50}N_3O_2Li = 83$ atoms), the initial geometry optimizations were initially carried out at the STO-3G level and refined at the HF/3-21G level.[8] While this theoretical level sometimes gives unsatisfactory relative energies, it is known that it usually gives quite good geometries.[9] Of the four structures examined, the lowest energy complex **3**, depicted in Figure 2, had the shortest distance (3.10 Å) between the

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