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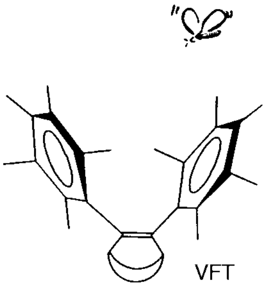
An Efficient Venus Flytrap for the Reversible Binding of Nitric Oxide[**]

Rajendra Rathore, Sergey V. Lindeman, and
Jay K. Kochi[*]

Intermolecular noncovalent binding of guest molecules by synthetic macromolecular hosts has been a rapidly growing field of research[1] since the first discovery of crown ethers by Pedersen.[2] The unique chemical and physical properties of these novel host–guest structures are the key to the future development of nanomolecular devices, chemosensors, etc.[3] Here we describe the synthesis of a novel *cis*-stilbenoid hydrocarbon ligand which strongly binds a neutral diatomic molecule such as nitric oxide (NO), which is of significant biological interest.[4]

The hydrocarbon ligand 1,2-bis(pentamethylphenyl)bicyclo[2.2.2]oct-2-ene (Venus flytrap, VFT)[5] possesses a unique molecular structure in which a pair of pentamethylphenyl moieties are forced to be closely juxtaposed in a cofacial manner by the very rigid bicyclooctene framework, as established by X-ray crystallography.[6]



VFT

The activation of VFT by oxidation in dichloromethane readily generates the persistent cation radical VFT$^{+\bullet}$,[7] which upon exposure to gaseous nitric oxide leads immediately to a bright blue solution. Quantitative IR spectroscopic analysis of the blue solution indicates the complete uptake of nitric oxide, as judged by observing the characteristic absorption at 1885 cm^{-1} for a single N–O stretching frequency.[8] The high stability of blue [VFT·NO]$^+$ allows the ready isolation of a single crystal from a mixture of dichloromethane and toluene at $-23\,^\circ$C. X-ray crystallography established its molecular structure to be made up of a single molecule of nitric oxide trapped between two cofacial phenyl rings. The diatomic nitric oxide fits neatly within the cavity of VFT, where it lies parallel to one of the phenyl rings, as shown by the space-filling representation in Figure 1.

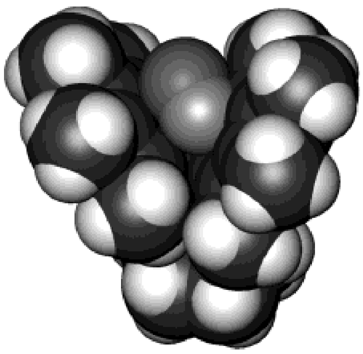


Figure 1. Space-filling representation of NO tightly entrapped within the VFT cleft.

The N–O bond distance of 1.12 Å in [VFT·NO]$^+$ is consistent with a noncovalently bonded nitric oxide molecule,[9] especially since the separation between the nitrogen atom and any aromatic carbon atom (av 2.5 Å) is much greater than the covalent N–C bonding distance.[10] Moreover, most of the positive charge resides on the aromatic and olefinic carbon atoms, as judged by the significant lengthening of the average C_{arene}–C_{arene} distance (1.42 Å) with respect to that in the neutral stilbenoid ligand.[11] Thus, VFT acts as a molecular tweezer for neutral NO. This is readily apparent upon inspection of the phenyl rings, which are significantly arched in an attempt to encapsulate the NO molecule. The distortion of the pentamethylphenyl groups is shown in Figure 2.[12]

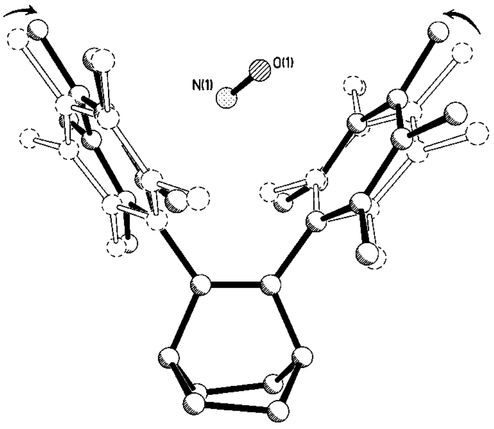


Figure 2. The superimposed molecular structures of the neutral stilbenoid ligand VFT (dashed line) and [VFT·NO]$^+$ (solid line); hydrogen atoms have been omitted for clarity.[12]

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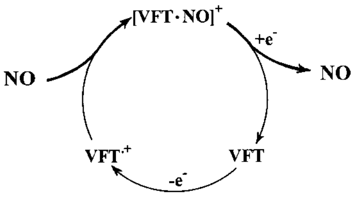
The tight binding of nitric oxide in [VFT·NO]$^+$ is also evident from the very high value of the binding constant K ($>3\times10^6\,\mathrm{M}^{-1}$) estimated by an electrochemical method;[13] this value is unprecedented for nitric oxide incarceration. Furthermore, the unusual stability is further reflected in the fact that NO cannot be extricated, even upon prolonged pumping in vacuo.

The same blue [VFT·NO]$^+$ is also obtained by mixing the neutral VFT ligand with the nitrosonium cation (NO$^+$) in dichloromethane at 25 °C.[14] Indeed, the two possibilities for the synthesis of [VFT·NO]$^+$ by treatment of either VFT$^{+\cdot}$ with gaseous NO or the neutral hydrocarbon (VFT) with the cationic NO$^+$ suggests the construction of a redox-controlled molecular pump for nitric oxide. The electrochemical (one-electron) reduction[13] of blue [VFT·NO]$^+$ rapidly leads to the neutral VFT and nitric oxide.[15] Scheme 1 presents the catalytic cycle for the reversible uptake and release of NO, which can be repeated indefinitely.[16]



Scheme 1. Reversible binding of NO by VFT.

We have successfully demonstrated the redox-controlled and exceptionally effective binding of neutral diatomic NO by the stilbenoid hydrocarbon ligand VFT. The nature of the unusually strong intermolecular binding in [VFT·NO]$^+$ is currently under investigation.

Experimental Section

2,3-Bis(pentamethylphenyl)bicyclo[2.2.2]oct-2-ene (VFT) was synthesized by the reaction of pentamethylphenylmagnesium bromide with 2,3-dibromobicyclo-[2.2.2]oct-2-ene in the presence of a palladium catalyst according to a known general procedure.[17] Yield: 94 %; m.p. 239–240°C (EtOH); ^{1}H NMR (CDCl$_3$): $\delta=1.77$ (br d, $J=7.4$ Hz, 4H), 1.91 (br d, $J=7.4$ Hz, 4H), 2.14 (s, 12H), 2.18 (s, 6H), 2.19 (s, 12H), 2.63 (br s, 2H); ^{13}C NMR (CDCl$_3$): $\delta=16.63$, 16.81, 19.83, 27.28, 37.79, 131.96, 132.08, 132.54, 139.45, 142.71; GC-MS: $m/z=400$ (M^+), calcd for $C_{30}H_{40}$: 400; elemental analysis calcd for $C_{30}H_{40}$: C 89.94, H 10.06; found: C 89.77, H 10.01. Crystal data for [VFT·NO]$^+$: ($C_{30}H_{40}$)NOSbCl$_6$. A suitable crystal ($0.2\times0.2\times0.1$ mm) was obtained by slow diffusion of toluene into a solution of blue [VFT·NO]$^+$ in dichloromethane at −23 °C. $M_r=765.08$, monoclinic, space group $P2_1/n$, $a=11.260(2)$, $b=20.084(2)$, $c=15.322(3)$ Å, $\rho_{\mathrm{calcd}}=1.549\,\mathrm{mg\,m^{-3}}$, $V=3280.9(11)$ Å^3, $Z=4$. The data were collected on a Siemens SMART diffractometer equipped with a CCD detector using Mo$_{K\alpha}$ radiation ($\lambda=0.71073$ Å) at −150 °C. A total of 40937 reflections were measured, of which 14952 were symmetrically nonequivalent. The structure was solved by direct methods and refined by the full-matrix least-squares procedure. Final residuals were $R_1=0.0496$ and $wR_2=0.0838$ for 14952 reflections with $I>2\sigma(I)$. The X-ray structure of dichloromethane monosolvate [VFT·NO$^+$SbCl$_6^-$·CH$_2$Cl$_2$] was also determined, and the details of the investigation can also be obtained from the Cambridge Crystallographic Data Centre. Crystal data for 1,2-bis(pentamethylphenyl)bicyclo[2.2.2]oct-2-ene: $C_{30}H_{40}$. A crop of well-formed crystals was obtained from ethanol/dichloromethane after three days at −23 °C. A colorless crystal of dimensions $0.3\times0.2\times0.1$ mm was used for the X-ray study. $M_r=400.62$, monoclinic, space group $P2_1/n$, $a=8.6608(7)$, $b=13.2230(10)$, $c=20.401(2)$ Å, $\rho_{\mathrm{calcd}}=1.139\,\mathrm{mg\,m^{-3}}$, $V=2335.6(3)$ Å^3, $Z=4$. The data were collected as described above. A total of 8416 reflections were measured, of which 3237 were symmetrically nonequivalent. The structure was solved by direct methods and refined by the full-matrix least-squares procedure. Final residuals were $R_1=0.073$ and $wR_2=0.126$ for 3073 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 no. CCDC-101552, -101553, and -101554. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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[6] See also J. E. Gano, G. Subramaniam, R. Birnbaum, *J. Org. Chem.* **1990**, *55*, 4760. Also note that the double bond in VFT is completely entombed by the bicyclooctene framework and the vicinal phenyl groups (containing four *ortho* methyl groups), which render it completely inert toward a variety of electrophiles.

[7] The oxidation of VFT to the green cation radical ($\lambda_{\max}=342$, 424, 740, >1100 nm) can be carried out electrochemically at $E^0_{\mathrm{ox}}=1.27$ V versus the standard calomel electrode (SCE) and as well as chemically with either the stable cation radical of 9,10-dimethoxy-1,4:5,8-diethano-1,2,3,4,5,6,7,8-octahydroanthracene (R. Rathore, J. K. Kochi, *J. Org. Chem.* **1995**, *60*, 4399) or with a mixture of chloranil and methanesulfonic acid in dichloromethane (R. Rathore, J. K. Kochi, *Acta. Chem. Scand.* **1998**, *52*, 114).

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[11] In the neutral hydrocarbon (VFT), the average C$_{\mathrm{arene}}$–C$_{\mathrm{arene}}$ distance is 1.40 Å. In addition, the olefinic C$_1$–C$_2$ bond length of 1.33 Å in neutral VFT is increased to 1.37 Å in [VFT·NO]$^+$.

[12] The distortion of the phenyl rings in [VFT·NO]$^+$ is judged by the decrease in the dihedral angle between the mean planes of the phenyl rings from about 71.8° to 61.1° (or to 64.5° in the dichloromethane solvate) as well as a decrease in the interplanar separation between the centers of the phenyl rings from about 4.94 Å (4.89 and 4.99 Å for the two disordered positions in VFT) to 4.74 Å in [VFT·NO]$^+$ and 4.64 Å in the dichloromethane solvate. Furthermore, the *para* carbon atoms in the phenyl rings are bent outwards in neutral VFT, whereas in [VFT·NO]$^+$ they are bent towards each other.

[13] The binding constant for $[\mathrm{VFT}\cdot\mathrm{NO}]^+$ was estimated from the electrochemical reduction potential of $E^{\circ}_{\mathrm{red}} = 0.58$ V versus SCE (obtained by cyclic voltammetry in dichloromethane containing 0.2 M *n*-tetrabutylammonium hexafluorophosphate as supporting electrolyte) in comparison to that of $E^{\circ}_{\mathrm{red}} = 1.49$ V versus SCE for the uncomplexed NO^+ cation by applying the procedure described for the $[\mathrm{hexamethylbenzene}\cdot\mathrm{NO}]^+$ complex; see K. Y. Lee, D. J. Kuchynka, J. K. Kochi, *Inorg. Chem.* **1990**, *29*, 4196.

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[15] The neutral hydrocarbon ligand VFT and NO do not interact, as shown by the absence of any color change upon saturation of a solution of VFT in dichloromethane with gaseous nitric oxide.

[16] In Scheme 1, $+\mathrm{e}^-$ indicates the cathodic reduction of $[\mathrm{VFT}\cdot\mathrm{NO}^+]$ at $E^{\circ}_{\mathrm{red}} = 0.6$ V versus SCE, which leads to the release of nitric oxide and neutral VFT, whereas $-\mathrm{e}^-$ indicates anodic oxidation at $E^{\circ}_{\mathrm{ox}} = 1.27$ V versus SCE of VFT to the green cation radical followed by the uptake of NO to yield $[\mathrm{VFT}\cdot\mathrm{NO}]^+$ as a bright blue solution ($\lambda_{\mathrm{max}} = 349$, 581 nm). To our knowledge, there are no other nonbiological systems for the reversible binding of nitric oxide.

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