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Novel Arene Receptors as Nitric Oxide (NO) Sensors

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The binding/release kinetics (and thermodynamics) associated with nitric oxide are highly relevant to number of biological systems.[1] Although many studies have dealt with transition-metal complexes,[2] the question of the reversible, specific, and efficient binding of $NO^\bullet$ by different types of organic compounds generally remains open. We wish to show how suitable entry into this problem is revealed by the study of charge-transfer complexes of the nitrosonium acceptor (NO^+) with various aromatic donors (**ArH**)[3] since the intermolecular [1:1] complexes $[\mathbf{ArH},NO]^+$ are characterized by complete electron delocalization arising from strong donor/acceptor interactions.[4] Thus, they are spontaneously formed (barrierless) via either the binding of nitrosonium with aromatic donors or the equivalent binding of nitric oxide with their cation radicals owing to the coupled equilibria in eq 1,

$$\mathbf{ArH} + NO^+ \overset{K_1}{\rightleftarrows} [\mathbf{ArH},NO]^+ \overset{K_2}{\rightleftarrows} \mathbf{ArH}^{+\bullet} + NO^\bullet \tag{1}$$

where the overall equilibrium constant is $K_{ET} = K_1K_2$ and the Nernst relationship defines the free-energy change: $\Delta G_{ET} = F\,(E^\circ_{ox} - E^\circ_{red})$.[5]

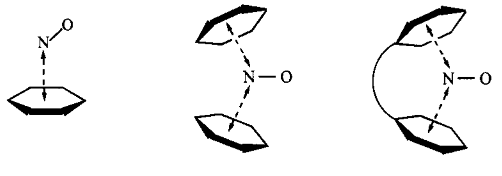
We now find that the corresponding [2:1] complexes are formed at high arene concentrations. Successful isolation and single-crystal X-ray crystallography establish the novel sandwich structure **II**, which is graphically depicted in Chart 1 together with the "open-face" sandwich structure **I** of the [1:1] complex.[4]

The unusual cofacial arrangement in **II** is quite reminiscent of bis-arene complexes of the transition metals; and interring connections of the arene ligands as in **III** optimize the chelate effect for effective binding of nitric oxide.[6] Indeed, the addition of diarene ligands ($\mathbf{Ar}_2$ in Chart 2) to even dilute solutions of the nitrosonium acceptor in dichloromethane immediately results in intense purple colorations with spectral bands near 340 nm and in the 450−600-nm region similar to those of monoarene complexes.[3] The linear dependence of the band intensities on nitrosonium concentration indicates that the set of coupled equilibria in eq 2 is greatly shifted to the intermolecular complex **III**.

$$\mathbf{Ar_2} + NO^+ \overset{K_1}{\rightleftarrows} [\mathbf{Ar_2},NO]^+ \overset{K_2}{\rightleftarrows} \mathbf{Ar_2}^{+\bullet} + NO^\bullet \tag{2}$$

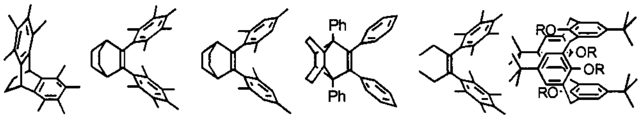
The extinction coefficients of the UV−vis bands evaluated from the absorption intensities, and the equilibrium constant K_1 determined by the competition method,[4] together with K_2 for the dissociative equilibrium and K_{ET} for the overall equilibrium, in eq 2 are listed in Table 1. It is important to note that both K_1 and K_2^{-1} for di-arenes are generally 10^3 larger than those for the correspondingly substituted monoarenes.[3e]

Chart 1



I **II** **III**

Chart 2



MEA **ST1** **ST2** **ST3** **ST4** **CAL**

Table 1. UV−Vis Spectral Data and Equilibrium Constants[a]

diarene	E^0_{ox}	$\lambda\ (\epsilon)^b$		$K_1\ (M^{-1})^c$	$K_2\ (M)^c$	K_{ET}
MEA	1.46	334 (7.8)	510 (1.5)	1.3×10^6	1.7×10^{-6}	2.1
ST1	1.35	345 (4.6)	590 (5.3)	1.3×10^7	1.3×10^{-5}	170
ST2	1.45	350 (6.6)	535 (4.5)	5.0×10^5	6.5×10^{-6}	3.3
ST3	1.55	360 (5.0)	460 (5.1)			
ST4	1.47	345 (4.0)	575 (5.8)	5.0×10^7	3.0×10^{-8}	1.5
CAL	1.45		538 (8.5)	2.0×10^8	1.6×10^{-8}	3.2

[a] In dichloromethane at 22 °C. [b] Wavelength λ in nm, extinction coefficient $\epsilon \pm 0.2$ in $10^3\ M^{-1}\ cm^{-1}$. [c] ±30%.

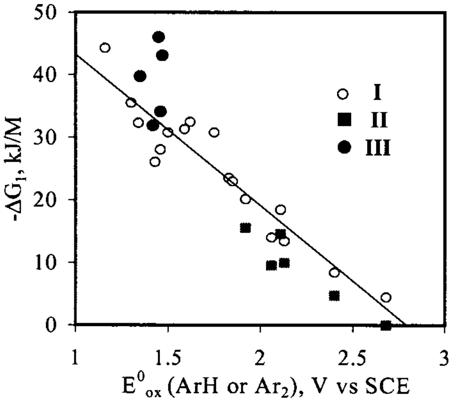


Figure 1. Dependence of free energy of complex formation on the oxidation potential of various aromatic donors.

The linear plot in Figure 1 shows the direct relationship of the free energy for complex formation with the oxidation potential of various arene donors. Most importantly, consideration of the three-state equilibria in eqs 1/2 indicates that those systems with weak arene donors ($E^\circ_{ox} > 1.5$ V) favor the diamagnetic reagents (**ArH** and NO^+). By contrast, the relatively electron-rich donors ($E^\circ_{ox} < 1.5$ V) favor the equlibrium shift to the paramagnetic species ($\mathbf{ArH}^{+\bullet}$ and $NO^\bullet$), and the CT complex is only observed at low temperatures. Complex formation is optimized at the isergonic point, and this is

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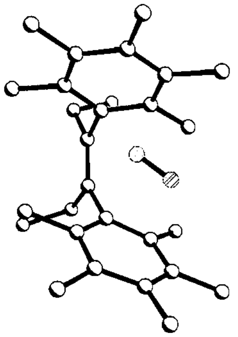

Figure 2. Molecular structure of the diarene complex [**ST4**,NO]$^+$ with all hydrogens omitted for clarity.

theoretically confirmed by the LCAO-MO description of the CT complex showing maximum electronic (donor/acceptor) coupling when E^o_{ox}(arene) $\approx$ E^o_{red}(NO$^+$) = 1.5 V vs SCE.[4] Thus, the best choice for nitrosonium/nitric oxide complexation based solely on *electronic* factors lies with aromatic donors having $E^o_{ox} \approx 1.5$ V, and this requirement is satisfied by the diarenes (Table 1). Since Figure 1 shows that the free-energy gain upon complex formation is much higher with diarenes than those with monoarenes of comparable E^o_{ox} value, it is clear that *structural* factors must also be evaluated.

X-ray structural analysis reveals that a single molecule of nitric oxide penetrates deeply within the rather narrow cleft formed by two cofacial aromatic moieties.[6] As a result, the diarene complexes must be structurally akin to the [2:1] complexes **II**. However, Figure 1 shows that the free-energy gain in [2:1] complexes is substantially less than that from the corresponding diarene complexes, and this supports the importance of the chelate effect—as manifested both in the enthalpy gain from multibond formation as well as an entropy loss from one-ligand coordination.[7] Moreover for maximum chelating effect, the binding of the multidentate ligand must also be organized so that the coordinating (NO) center is encapsulated with minimal (distortional) penalty (Figure 2). It is also significant that NO lies within the undistorted calixarene complex [**CAL**,NO]$^+$ equidistant from the cofacial aromatic planes at an optimal distance of $d = 2.55$ Å,[6a] as established by the X-ray structures of the [2:1] complexes of toluene ($d = 2.5$ Å) and *o*-xylene ($d = 2.6$ Å).[4b] In the other diarene complexes the two distances are nonequivalent, indicating the second bond provides some additional free-energy gain, but the rather rigid structure of the stilbenoid ligands (**ST**1−4) as well as the dihydroanthracene analogue **MEA** do not allow optimal placement of the aromatic ring for NO binding. [For example, $d = 2.15$ and 3.10 Å in [**MEA**,NO]$^+$, $d = 2.24$ and 2.70 Å in [**ST1**,NO]$^+$, and $d = 2.15$ and 2.90 Å in [**ST4**,NO]$^+$ shown in Figure 2. As a result **CAL** forms the most stable NO complex (Table 1).

The enhanced formation constants of diarene complexes ensure high sensitivity and specificity for NO binding. These together with large extinction coefficients of the visible absorption bands allow selective NO sensors to be designed on the basis of the coupled equilibria in eq 2. For example, colorless (CH_2Cl_2) solutions of either **CAL** or **ST4** with some added oxidant (e.g., PbO_2 or Et_3OSbCl_6) persist unchanged for prolonged periods.[8] However, immediately upon the exposure to nitric oxide (gas), the colorless solutions take on an intense purple coloration (see left table of contents graphic) diagnostic of the diarene complexes (Figure 3). The same color change is observed in the solid state with a mull prepared as an intimate mixture of **CAL** and PbO_2. Exposure of such a coated (pale gray) alumina plate to nitric oxide produces the dramatic color change (see right table of contents graphic) which is completely reversible simply by NO entrainment with a mild air stream or upon evacuation. We are presently also investigating a (tunable) electrochemical sensor based on the same basic principle.

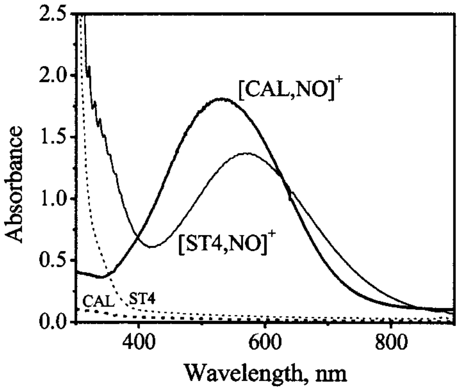

Figure 3. Spectral changes upon the addition of nitric oxide to Ar_2/oxidant systems. [Dashed lines are before and solid lines are after NO addition.]

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Supporting Information Available: Experimental details together with the X-ray crystallographic data and ORTEP diagrams for the [2:1] complexes: [(toluene)$_2$,NO]$^+$SbCl$_6^-$ and [(*o*-xylene)$_2$,NO]$^+$SbCl$_6^-$ and the diarene complexes [**ST4**,NO$^+$]SbCl$_6^-$ and [**MEA**,NO$^+$]SbCl$_6^-$ (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) For some recent studies, see: (a) Laverman, L. E.; Ford, P. C. *J. Am. Chem. Soc.* **2001**, *123*, 11614. (b) Laverman, L. E.; Wanat, A.; Oszajca, J.; Stochel, G.; Ford, P. C.; van Eldik, R. *J. Am. Chem. Soc.* **2001**, *123*, 9780. (c) Wolak, M.; Zahl, A.; Schneppensieper, T.; Stochel, G.; van Eldik, R. *J. Am. Chem. Soc.* **2001**, *123*, 285. (d) Andersen, J. F.; Ding, X. D.; Balfour C.; Shokhireva, T. K.; Champagne, D. E.; Walker, F. A.; Montfort, W. R. *Biochemistry* **2000**, *39*, 10118. (e) Adachi, H.; Sonoki, H.; Hoshino, M.; Wakasa, M.; Hayashi, H.; Miyazaki, Y. *J. Phys. Chem.* **2001**, *105*, 392.

(2) Compare: (a) Hoshino, M.; Laverman, L.; Ford, P. C. *Coord. Chem. Rev.* **1999**, *187*, 75. (b) Sellmann, D.; Blum, N.; Heinemann, F. W.; Hess, B. A. *Chem. Eur. J.* **2001**, *7*, 1874.

(3) (a) Reents, W. D., Jr.; Freiser, B. S. *J. Am. Chem. Soc.* **1980**, *102*, 271. (b) Brownstein, S.; Gabe, E.; Lee, F.; Tan, L. *J. Chem. Soc., Chem. Commun.* **1984**, 1566. (c) Brownstein, S.; Gabe, E.; Lee, F.; Piotrwski, A. *Can. J. Chem.* **1986**, *64*, 1661. (d) Brownstein, S.; Gabe, E.; Louie, B.; Piotrowski, A. *Can. J. Chem.* **1987**, *65*, 1661. (e) Kim, E. K.; Kochi, J. K. *J. Am. Chem. Soc.* **1991**, *113*, 4962. For a recent review, see: Borodkin, G. I.; Shubin, V. G. *Russ. Chem. Rev.* (*Engl. Transl.*) **2001**, *70*, 211.

(4) (a) Rosokha, S. V.; Kochi, J. K. *J. Am. Chem. Soc.* **2001**, *123*, 8985. (b) For experimental details and the X-ray structures of various **II** and **III** complexes, see Supporting Information.

(5) E^o_{ox} is the reversible oxidation potential of arene donors, and E^o_{red} the reduction potential of NO$^+$.

(6) (a) Rathore, R.; Lindeman, S. V.; Rao, K. S.; Sun, D.; Kochi, J. K. *Angew. Chem., Int. Ed.* **2000**, *39*, 2123. (b) Rathore, R.; Kochi, J. K. *J. Org. Chem.* **1998**, *63*, 8630.

(7) For the thermodynamics of the chelate effect, see: Cotton, F. A.; Wilkinson, G. *Advanced Inorganic Chemistry*, 5th ed.; Wiley: New York, 1988.

(8) (a) Particularly in nonaqueous solutions. (b) Note that this procedure circumvents the kinetic lability of arene cation radicals. (c) From the results in Table 1 (eq 2), we estimate the intrinsic NO sensitivity to be ~1 μM on the basis of a spectrophotometric resolution of 0.01 in the optical density; however, for a solid-state device the practical sensitivity will depend on its design, particularly for application to an aqueous environment.

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