Electrochemical Control of Recognition Processes. A Three-Component Molecular Switch

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In recent years, considerable interest has been devoted to the creation of organic based *molecular devices*[1] that have the potential to function as information storage/switching systems[2] in molecular scale computers[3] and other applications.[4] To this end, a number of devices have been constructed, including molecular shuttles, switches, and wires.[5]

Biological systems use the interplay of redox and molecular recognition to regulate a wide variety of processes and transformations. In our continued efforts to understand these systems, we have designed synthetic receptors where non-covalent interactions (hydrogen-bonding and aromatic stacking) have been demonstrated to modulate the redox potentials of flavin cofactors.[6] Using these receptors, we have established that the flavin radical anion is stabilized by hydrogen bonding. Concurrent with this stabilization, we observed enhanced recognition of the radical anion relative to the fully oxidized flavin.[6a] This effect was quantified in an analogous system by Smith and co-workers.[7] In recent studies, we have observed destabilization of the flavin radical anion by aromatic stacking.[6b]

The opposite effects of hydrogen bonding and aromatic stacking on flavin reduction potentials suggest a complementarity in the modulation of recognition upon redox state change. To examine this effect and explore the control of molecular recognition through redox processes, we have created a system where the competition between two hosts is regulated by the redox state of the guest. The two hosts used in this study were anthracene receptor **A** and acylated diaminopyridine receptor **D**. Both hosts can undergo three-point hydrogen-bonding interactions with guest naphthalimide, either in its oxidized $\mathbf{N_{ox}}$ or radical anion $\mathbf{N_{rad}{}^-}$ form (Figure 1). In addition, host **A** is capable of forming aromatic stacking interactions. We report here redox-controlled recognition in this system and the creation of a three-component, two-pole, molecular switch (Figure 2).
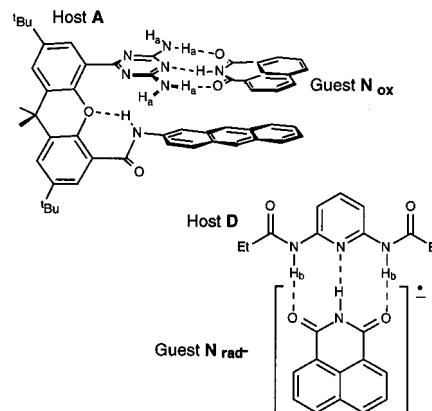
Figure 1. Naphthalimide $\mathbf{N_{ox}}$ bound to anthracene receptor **A** and naphthalimide radical anion $\mathbf{N_{rad}{}^-}$ bound to acylated diaminopyridine receptor **D**.
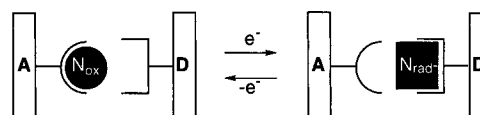
Figure 2. Schematic of redox-mediated recognition.

In our initial studies, we determined the thermodynamic constants for the isolated two-component systems. Association constants (K_a) of $\mathbf{N_{ox}}$ with **A** and **D** were obtained via NMR titration experiments in CDCl$_3$ (Table 1).[8] It was found that **A** binds $\mathbf{N_{ox}}$ more than an order of magnitude stronger than **D**, due to favorable aromatic−aromatic interactions.

To quantify the binding of $\mathbf{N_{rad}{}^-}$, we investigated the change in standard reduction potential ($E_{1/2}$) of $\mathbf{N_{ox}}$ upon addition of **A** and **D**. Addition of **D** resulted in a significant shift of $E_{1/2}$ to less negative values, indicating substantial stabilization of the radical anion. Addition of **A**, in contrast, had little effect on the reduction potential of naphthalimide (Table 1). This results from the offsetting favorable effect of hydrogen bonding and unfavorable effect of aromatic stacking on the reduction process. Using the association constants (K_a) and $E_{1/2}$ values, it is possible to construct thermodynamic squares for the two host−guest systems (Figure 3).[9]

The thermodynamic squares in the front and rear describe the molecular recognition and redox reactions of $\mathbf{N_{ox}}$ and $\mathbf{N_{rad}{}^-}$ in the presence of **D** and **A** respectively. The ΔG_3 and $\Delta G_{3'}$ values were calculated algebraically using those derived from experimentally determined K_a and $E_{1/2}$ values. From the *redox cube* obtained by combining these thermodynamic squares, it is apparent that $\mathbf{N_{ox}}$ has a large preference for **A** while $\mathbf{N_{rad}{}^-}$ interacts more strongly with **D**.

We verified the predicted preference in the oxidized state by titrating $\mathbf{N_{ox}}$ with a 1:1 mixture of **A** and **D**. In the NMR, a large downfield shift of the amino protons of **A** and virtually no shift of the amide protons of **D** were observed (Figure 4). The binding preference of $\mathbf{N_{rad}{}^-}$ was verified using simultaneous electrochemistry and EPR (SEEPR).[11] Hydrogen bonding of **D** to $\mathbf{N_{rad}{}^-}$ results in significant spectral changes due to alteration

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(9) K_a and $E_{1/2}$ values were determined in similar noncompetitive solvents (CDCl$_3$ and CH$_2$Cl$_2$) chosen due to their attributes for NMR and electrochemical experiments, respectively. It was found that the presence of carrier electrolyte does not affect the association constants.

(10) Due to the low solubility of the anthracene receptor **A**, only 5 equiv were added. Since the observed changes in $E_{1/2}$ are small, the values obtained at this concentration should be quite close to the limiting reduction potential.

(11) For a description of the SEEPR cell see: Niemz, A.; Imbriglio, J.; Rotello, V. *J. Am. Chem. Soc.* **1997**, *119*, 887.

Table 1. Binding Constants, Reduction Potentials, and Energetics for Redox Cube

process	K_a (M^{-1})^a	$E_{1/2}$ (mV)^{b,c}	ΔG (kcal/mol)
$\mathbf{D} + \mathbf{N_{ox}} \rightarrow [\mathbf{D \cdot N_{ox}}]$	150 ± 1		$\Delta G_1 = -2.95 \pm 0.01$
$[\mathbf{D \cdot N_{ox}}] \rightarrow [\mathbf{D \cdot N_{rad}}^-]$		-1657 ± 1^e	$\Delta G_2 = 38.21 \pm 0.02$
$\mathbf{D} + \mathbf{N_{rad}}^- \rightarrow [\mathbf{D \cdot N_{rad}}^-]$	41000 ± 3000^d		$\Delta G_3 = -6.24 \pm 0.05^d$
$\mathbf{D} + \mathbf{N_{ox}} \rightarrow \mathbf{D} + \mathbf{N_{rad}}^-$		-1800 ± 2	$\Delta G_4 = 41.51 \pm 0.05$
$\mathbf{A} + \mathbf{N_{ox}} \rightarrow [\mathbf{A \cdot N_{ox}}]$	1840 ± 280		$\Delta G_{1'} = -4.42 \pm 0.09$
$[\mathbf{A \cdot N_{ox}}] \rightarrow [\mathbf{A \cdot N_{rad}}^-]$		-1802 ± 4^f	$\Delta G_{2'} = 41.56 \pm 0.09$
$\mathbf{A} + \mathbf{N_{rad}}^- \rightarrow [\mathbf{A \cdot N_{rad}}^-]$	1700 ± 350^d		$\Delta G_{3'} = -4.37 \pm 0.14^d$
$\mathbf{A} + \mathbf{N_{ox}} \rightarrow \mathbf{A} + \mathbf{N_{rad}}^-$		-1800 ± 2	$\Delta G_{4'} = 41.51 \pm 0.05$

^{a} CDCl$_3$, 23 °C, imide peak followed. ^{b} In CH$_2$Cl$_2$, tetrabutylammonium perchlorate carrier (0.1 M), $[\mathbf{N_{ox}}] = 1 \times 10^{-3}$ M, 23 °C. ^{c} Referenced to ferrocene as an internal standard. ^{d} Calculated according to $\Delta G_1 + \Delta G_2 + (-\Delta G_3) + (-\Delta G_4) = 0$; $\Delta G_3 = \Delta G_1 + \Delta G_2 - \Delta G_4$. ^{e} Host added until limiting value was reached, $[\mathbf{D}] = 4 \times 10^{-2}$ M. $^f [\mathbf{A}] = 5 \times 10^{-3}$ M.[10]
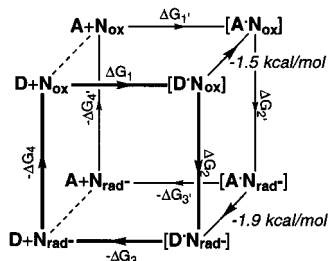
Figure 3. Redox cube predicting redox-specific binding.
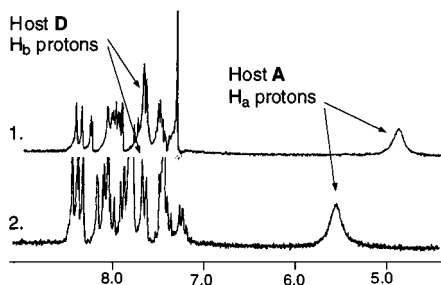
Figure 4. ^{1}H NMR spectra showing a 1:1 host mixture of $\mathbf{A}$ and $\mathbf{D}$ in the absence (1) and presence (2) of $\mathbf{N_{ox}}$ guest.

Figure 5. SEEPR in CH$_2$Cl$_2$, tetrabutylammonium perchlorate carrier (0.1 M), $[\mathbf{N_{ox}}] = 10^{-3}$ M, low-field half of SEEPR spectra: (a) $\mathbf{N_{rad}}^-$; (b) $\mathbf{N_{rad}}^- + \mathbf{A}$, $[\mathbf{A}] = 10^{-2}$ M; (c) $\mathbf{N_{rad}}^- + \mathbf{D}$, $[\mathbf{D}] = 10^{-2}$ M; (d) $\mathbf{N_{rad}}^- + \mathbf{A} + \mathbf{D}$, $[\mathbf{A}] = [\mathbf{D}] = 10^{-3}$ M.
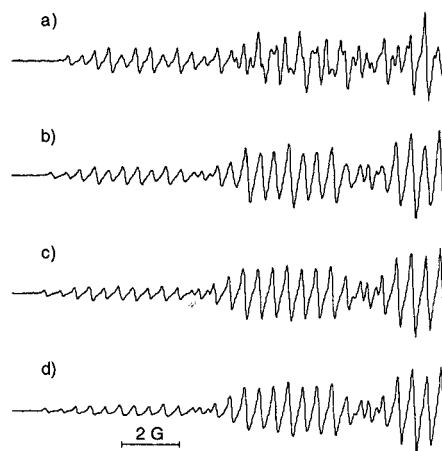
of the hyperfine coupling constants (Figure 5).[12] Complexation by $\mathbf{A}$ also perturbs the spin density in a characteristic way, leading to a distinctive spectrum. If $\mathbf{N_{rad}}^-$ is present in different forms (unbound, bound to receptor $\mathbf{A}$ or $\mathbf{D}$), the resulting spectrum is a superposition of the spectra of these forms in the appropriate ratios, which can be quantified through spectrum simulation and iterative curve-fitting.[13] The spectrum resulting from bulk electrolysis of a 1:1:1 mixture of $\mathbf{N_{ox}}$, $\mathbf{A}$, and $\mathbf{D}$ indicates a 87:13 ratio preference of $\mathbf{N_{rad}}^-$ for binding to $\mathbf{D}$, validating our predictions.[14]

The increase in binding strength with $\mathbf{D}$ is due to an increase in charge density on the carbonyl oxygens of naphthalimide $\mathbf{N_{ox}}$ upon reduction of $\mathbf{N_{ox}}$ to $\mathbf{N_{rad}}^-$, leading to stronger hydrogen-bonding interactions. The unaltered binding strength with $\mathbf{A}$ upon reduction of $\mathbf{N_{ox}}$ to $\mathbf{N_{rad}}^-$ is due to offsetting changes in hydrogen-bonding and aromatic-stacking effects. In the $\mathbf{A}-\mathbf{N}$ complex, the favorable aromatic-stacking interactions between the electron-poor $\mathbf{N_{ox}}$ and the electron-rich $\mathbf{A}$ are converted to unfavorable stacking interactions between the electron-rich $\mathbf{N_{rad}}^-$ and the electron-rich $\mathbf{A}$.

In summary, we have demonstrated host selection through choice of guest redox state. This system provides a three-component, two-pole, molecular switch where the recognition process can be controlled electrochemically. Applications of this molecular switch toward the creation of an electrochemical read–write system are underway and will be reported in due course.

Supporting Information Available: ^{1}H NMR titration data, cyclic voltammograms and SEEPR spectra (experimental and simulated) (16 pages). See any current masthead page for ordering and Internet access instructions.

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(14) Since bulk electrolysis is not exhaustive, the concentration of naphthalimide radical anion $\mathbf{N_{rad}}^-$ is lower than the concentration of naphthalimide $\mathbf{N_{ox}}$.