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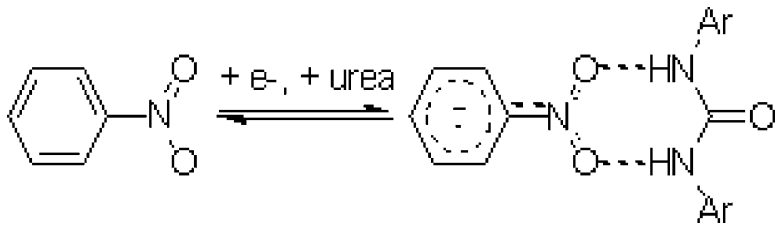

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Electrochemically Controlled Hydrogen Bonding. Nitrobenzenes as Simple Redox-Dependent Receptors for Arylureas

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Abstract: Reduction of nitrobenzene derivatives in the presence of arylureas in aprotic solvents results in large positive shifts in potential of the nitrobenzene$^{0/-}$ cyclic voltammetry wave with little change in wave shape. This behavior is indicative of reversible hydrogen bonding between nitrobenzene radical anions and arylureas. Computer fitting of the cyclic voltammetry of 4-nitroaniline, NA, plus 1,3-diphenylurea in DMF shows essentially no binding between urea and NA in the oxidized state ($K_{ox} < 1$ M^{-1}), but very strong binding in the reduced state ($K_{red} = 8 \times 10^4$ M^{-1}), along with very rapid rates of hydrogen bond formation (k_f's $\approx 10^8$–10^{10} M^{-1} s^{-1}), making this system a fast on/off redox switch.

Introduction

One of the important goals of supramolecular chemistry is the development of externally controlled systems, that is, well-defined molecular aggregates or "supramolecules" whose structure or other physical property can be changed or "switched" in a predictable manner by an external signal. Like all aspects of supramolecular chemistry, this endeavor is inspired by biological chemistry where structural changes caused by external signals are essential to the communication and coordination between molecules required for life. In a similar fashion, some means of external control will be essential to all higher functions envisioned for synthetic supramolecular systems, including sensors,[1] molecular electronics,[2] and molecular machines.[3]

The importance of this aspect of supramolecular chemistry has been recognized for some time, and there are now numerous examples of synthetic supramolecular switches that respond to a wide variety of signals, including electrons, photons, and other chemicals.[4−6] In all cases, the key to a successful switch is that the external signal strongly perturbs an important binding interaction holding together the supramolecular complex. Because one of the most important binding interactions is hydrogen bonding,[7] it is not surprising that a number of switches that function via perturbation of hydrogen bonding have been constructed,[8] including some excellent examples of redox-switched hydrogen bonding.

However, despite this success, if we define a good switch as one in which the external signal changes the binding strength by at least a factor of 10, then the number of good redox switches for organic molecular systems is still rather limited. Indeed, in the case of molecular redox switches that depend on hydrogen bonding, the successful switches all rely on one of four redox couples. As outlined in Scheme 1, these are (a) flavins, **1**, with diamidopyridines, **2**, or diaminotriazines as the binding partners,[9] (b) arylimides (most often naphthalimide, **3**) with the same binding partners as the flavins[10a−e] or with thioureas,[10f] (c) *o*-quinones, **4**, with arylureas, **5**,[9f,10a,11] and (d)

(1) For reviews, see: (a) Goldenberg, L. M.; Bryce, M. R.; Petty, M. C. *J. Mater. Chem.* **1999**, *9*, 1957−1974. (b) Fabbrizzi, L.; Poggi, A. *Chem. Soc. Rev.* **1995**, 197−202.
(2) For a recent review, see: Carroll, R. L.; Gorman, C. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 4378−4400.
(3) See reviews in: *Acc. Chem. Res.* **2001**, *34* (Special Edition on Molecular Machines).
(4) For reviews that focus primarily on redox-controlled supramolecular systems in solution, see: (a) Beer, P. D.; Gale, P. A.; Chen, Z. *Adv. Phys. Org. Chem.* **1998**, *31*, 1−89. (b) Boulas, P. L.; Gomez-Kaifer, M.; Echegoyen, L. *Angew. Chem., Int. Ed.* **1998**, *37*, 216−247. (c) Kaifer, A. E. *Acc. Chem. Res.* **1999**, *32*, 62−71. (d) Tucker, J. H. R.; Collinson, S. R. *Chem. Soc. Rev.* **2002**, *31*, 147−156.
(5) For a recent review covering redox and photocontrolled supramolecular systems on surfaces, see: Cooke, G. *Angew. Chem., Int. Ed.* **2003**, *42*, 4860−4870.
(6) For reviews containing numerous examples of the use of electron, photon, and chemical signals to control position in interlocked supramolecular structures, see: (a) Ballardini, R.; Balzani, V.; Credi, A.; Gandolfi, M. T.; Venturi, M. *Acc. Chem. Res.* **2001**, *34*, 445−455. (b) Collin, J. P.; Dietrich-Buchecker, C.; Jimenez-Molero, M. C.; Sauvage, J. P. *Acc. Chem. Res.* **2001**, *34*, 477−487. (c) Amendola, V.; Fabbrizzi, L.; Mangano, C.; Pallavicini, P. *Acc. Chem. Res.* **2001**, *34*, 488−493.
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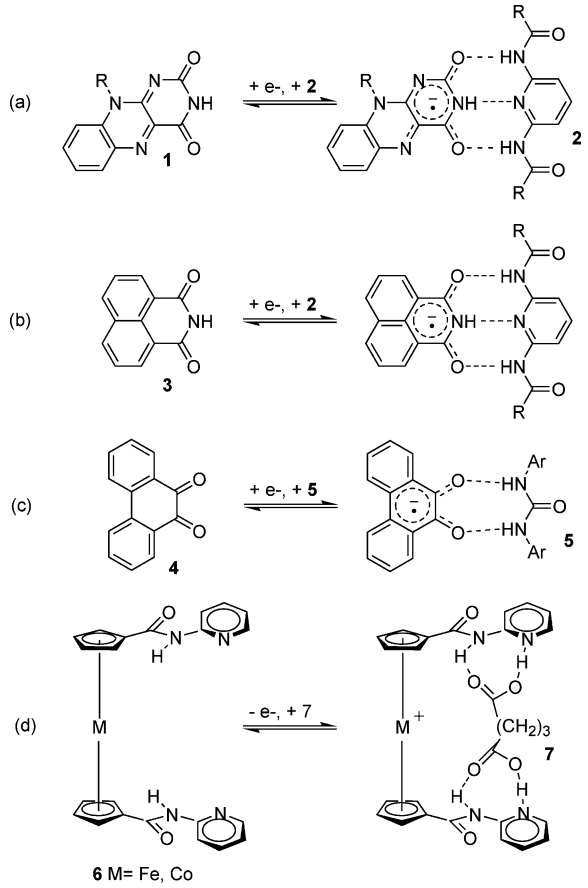
Scheme 1. Organic, Molecular, Redox-Dependent Hydrogen-Bonding Systems in Which There Is a >10-Fold Difference in Binding Strength between Oxidation States[a]



[a] The equations indicate which oxidation state of the receptor binds the substrate most strongly. However, with (a), (b), and (d), substantial binding occurs with the other oxidation state as well.

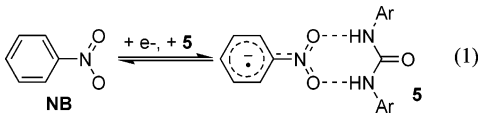
1,1′-diamide-substituted metallocenes, **6**, with dicarboxyllic acids (pictured) or cyclic ureas.[12]

The flavin system, reported by Rotello and co-workers in 1995,[9a] was the first example of strong, selective redox-dependent hydrogen bonding in an organic molecular system. Shortly thereafter, we reported the naphthalimide and *o*-quinone systems.[10a] Subsequently, all three systems have been modified and further studied by several groups. For example, Leigh and co-workers recently utilized the naphthalimide system to create the first molecular shuttle based on redox-dependent hydrogen bonding.[10e]

The above are not the only examples of redox-dependent hydrogen bonding that have been reported, but other organic molecular systems have shown only modest redox-dependence. The metallocene-based receptors are a case in point. There are numerous examples in which metallocenes (primarily ferrocene) have been incorporated as the redox-active component. This has worked quite well for the design of redox-dependent receptors for ions,[4a] but, to date, the 1,1′-diamide metallocenes reported by Tucker and co-workers[12] (Scheme 1, case d) are the only examples where a >10-fold difference in binding strength has been observed with nonionic guests.[13,14]

There also have been some interesting attempts to use the tetrathiofulvalene redox couple to perturb hydrogen-bonding interactions.[15] This redox couple has been used very successfully to perturb electrostatic interactions with ions and $\pi-\pi$ interactions with organic molecules,[16] but so far efforts to perturb hydrogen bonding interactions have only been modestly successful.

The above examples make it clear that designing strong, selective redox-dependent hydrogen bonds to molecules is not a trivial task. A review of the papers referenced above reveals a number of systems that look very promising, but in the end give only modest redox-dependence. It is also clear that, although some very interesting systems have been created with the redox couples listed in Scheme 1, further development in this field will require the introduction of additional redox couples that can strongly perturb hydrogen bonding to molecules. The purpose of this paper is to do just that. Specifically, we would like to introduce the nitrobenzene/diarylurea system, eq 1, as a new example of strong, selective, redox-dependent hydrogen bonding.



(1)

It is well established that nitro groups can act as hydrogen acceptors and form both intra- and intermolecular hydrogen bonds in solution[17] and in the solid state.[18] However, despite the Lewis structure, which places a formal negative charge on one of the oxygens in the nitro group, they are much poorer hydrogen acceptors than carbonyl oxygens or pyridyl nitrogens,[17−19] the acceptors commonly used to form well-defined, hydrogen-bonded complexes in solution. As a result, nitro groups are not typically used in the design of solution-phase supramolecular complexes.

On the other hand, like carbonyls, nitro groups are electron-withdrawing. When attached to aromatic rings, they facilitate the reduction of the aromatic to form a stable radical anion,

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(13) For some recent examples of interesting ferrocene-containing receptors that show modest redox-dependence with nonionic guests, see refs 9f, 12c and: Saweczko, P.; Enright, G. D.; Kraatz, H.-B. *Inorg. Chem.* **2001**, *40*, 4409−4419.

(14) Cooke and co-workers have recently reported very strong redox-dependent binding between ferrocene carboxylic acid and benzamidines: Cooke, G.; Duclairoir, F. M. A.; Kraft, A.; Rosair, G.; Rotello, V. M. *Tetrahedron Lett.* **2004**, *45*, 557−560. This is an interesting system that should find use in novel device-type applications. However, because initial proton transfer occurs to give the carboxylate anion and the benzamidinium cation, this is, arguably, also an example of a very good ferrocene-based ion receptor.

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(18) (a) Panunto, T. W.; Urbanczyk-Lipkowska, Z.; Johnson, R.; Etter, M. C. *J. Am. Chem. Soc.* **1987**, *109*, 7786−7797. (b) Allen, F. H.; Baalham, C. A.; Lommerse, J. P. M.; Raithby, P. R.; Sparr, E. *Acta Crystallogr., Sect. B* **1997**, *53*, 1017−1024. (c) Robinson, J. M. A.; Philp, D.; Harru, K. D. M.; Karicki, B. M. *New J. Chem.* **2000**, *24*, 799−806.

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and, like the flavins, imides, and *ortho*-quinones, this reduction increases the negative charge on the oxygens. The ability of nitroaromatics to be reversibly reduced to form stable radical anions with increased negative charge on oxygen was used with much success by Gokel, Echegoyen, and co-workers to prepare redox-dependent hosts for metal cations early on in the development of redox-dependent receptors.[20] In this work, we show that nitroaromatics can also be used with success to form redox-dependent hydrogen bonds to neutral molecules.

Experimental Section

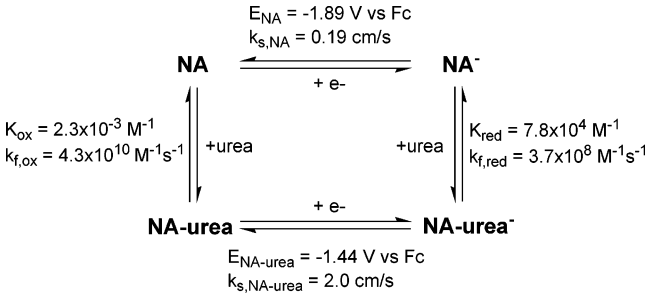
Reagents. 1,3-Di-(4-trifluoromethylphenyl)urea, 1-phenyl-3-propylurea, and 1-phenyl-3-dibutylurea were prepared from the appropriate isocyanates and amines using a previously described procedure.[11b] All other chemicals were purchased from commercial sources as reagent grade or better and were used without further purification with the following exceptions. *p*-Nitroaniline was recrystallized from ethanol and dried overnight in a vacuum oven at 100 °C. *p*-Nitrotoluene was recrystallized from methanol/water and dried under vacuum overnight at room temperature. *p*-Nitroanisole was recrystallized from hexane and dried under vacuum overnight at room temperature. 1,3-Diphenylurea was recrystallized from ethanol and dried overnight in a vacuum oven at 100 °C. Benzamide was recrystallized from ethanol and dried in a vacuum oven for 3 h at 60 °C. Tetrabutylammonium was recrystallized three times from 95% ethanol and dried overnight in a vacuum oven at 100 °C.

General Voltammetry Procedures. Cyclic voltammetry (CV) experiments were performed with a PAR model 263 digital potentiostat using the model 270 electrochemistry software package. The acquisition mode was set to "ramp" to simulate an analogue experiment. All measurements were conducted under N_2 in a jacketed, one-compartment cell with a Au or Pt disk working electrode (~2 mm diameter), a Pt wire counter electrode, and a Ag wire pseudo-reference electrode. The solvent, either CH_2Cl_2 (distilled from CaH_2) or anhydrous grade *N*,*N*-dimethylformamide (DMF), was passed through a column of activated alumina directly into the cell. NBu_4PF_6 (0.1 M) was used as the electrolyte. In most experiments, ferrocene (Fc) or decamethylferrocene (Fc*) (~1 mM) was also added as an internal potential reference. For the CVs used for computer simulation, ferrocene was not added. Instead, the Ag wire reference was placed in a separate compartment so the reference potential would not change when substrate was added. O_2 was removed from the electrolyte solution by bubbling N_2 through the solvent for several minutes prior to making a measurement. Temperature was controlled by using a circulating water bath to run 25 °C water through the outer cell jacket.

Voltammetric Titrations. To determine the equilibrium and rate constants associated with the redox-dependent binding, titration experiments were run in 0.1 M NBu_4PF_6/DMF using nitroaniline (NA) as the receptor and diphenylurea (urea) as the substrate. For these experiments, background CV's in the absence of NA and urea were recorded at four scan rates between 100 and 1500 mV/s. NA was then added to give a concentration of 1 mM, and a new set of CV's were run at the same scan rates. Next, the urea was added in increments from ~0.5 mM up to ~50 mM. CV's at the different scan rates were run after each addition.

CV Simulation. The background-subtracted CV's from the titration experiments were fit to the mechanism shown in Scheme 2 using the DigiSim program (v 3.03, BioAnalytical Systems). The formal redox potential of nitroaniline, E_{NA}, the diffusion coefficient, D, and the uncompensated resistance in the cell, R_u, were determined first by fitting the CV's with no added urea using Butler−Volmer kinetics and assuming that at these scan rates the voltammetry of NA should be completely reversible. The peak-to-peak separation was then fit by adjusting the R_u value. This resulted in R_u values of 800−1000 Ω.

Scheme 2. Equilibria Governing the Redox-Dependent Binding of Nitroaniline, NA, to Ureas



The E_{NA}, D, and R_u values determined in the above manner were then used to fit the CV's in the presence of urea using an iterative process. All species were assumed to have the same D. Initial experimentation indicated that the electron-transfer rate constants, k_s, had to be around 1 cm/s and the forward rate constants for hydrogen bonding, k_f, had to be around 1×10^9 M^{-1} s^{-1} to give good fits to the data. These parameters were initially set to these values, and then K_{ox} and K_{red} were varied to give the best fit to the experimental voltammograms (all urea concentrations and all scan rates). In the next iteration, the K_{ox} and K_{red} values were set to the results from the initial fitting and the k_s values varied to give the best fit to the experimental data. These two steps were repeated in sequence until no further change was observed. In the final step, the K_{ox}, K_{red}, and k_s values were set and the k_f values varied to give the best fit. The average results (80% confidence limits) from three separate experiments for all of the fitted parameters are as follows: $k_{s,NA} = 0.19 \pm 0.10$ cm/s, $k_{s,NA-urea} = 2.0 \pm 1.2$ cm/s, $K_{ox} = (2.3 \pm 3.4) \times 10^{-3}$ M^{-1}, $k_{f,ox} = (4.3 \pm 3.9) \times 10^{10}$ M^{-1} s^{-1}, and $K_{red} = (7.8 \pm 4.7) \times 10^4$ M^{-1}, $k_{f,red} = (3.7 \pm 2.9) \times 10^{10}$ M^{-1} s^{-1}. Note that, given the confidence limits, K_{ox} cannot be determined from these data, although it is clear that the value must be small.

Results and Discussion

Redox-dependent binding is most conveniently detected by looking at the voltammetry of the redox-active component (receptor) with and without its binding partner (substrate) present. Simply speaking, if the substrate binds more strongly to the oxidized form of the receptor, it makes it more difficult to reduce the receptor, and the half-wave potential, $E_{1/2}$, of the receptor shifts toward more negative potentials in the presence of the substrate. On the other hand, if the substrate binds more strongly to the reduced form of the receptor, it will be easier to reduce the receptor in the presence of the substrate, and the $E_{1/2}$ shifts toward more positive potentials.

Voltammetry of Nitrobenzene in the Presence of 1,3-Diphenylurea. Figure 1 shows cyclic voltammograms (CV's) of nitrobenzene (NB) in CH_2Cl_2 by itself (a) and in the presence of 10 mM 1,3-diphenylurea (b). The chemically reversible CV wave in the blank solution is due to $NB^{0/-1}$ redox couple. Upon addition of 1,3-diphenylurea, this wave decreases in size, broadens slightly, and, most significantly, shifts positive by 163 mV. If the potential is switched immediately after the cathodic peak (Figure 1b, −), the height of the return peak in the presence of 1,3-diphenylurea remains the same as the forward peak, indicating that the radical anion is stable under these conditions. This behavior is similar to that observed with the 9,10-phenanthrenequinone and naphthalimide systems and is consistent with reversible hydrogen bonding of the urea to the NB radical anion.

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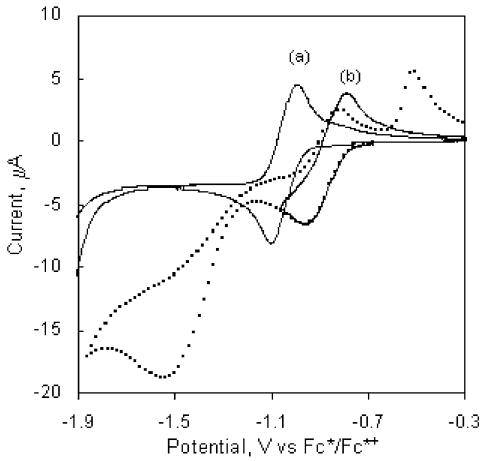


Figure 1. Cyclic voltammograms of 1 mM nitrobenzene, NB, in CH_2Cl_2 (a) by itself and (b) in the presence of 10 mM 1,3-diphenylurea. (b) −: Potential switched immediately after the NB reduction peak. (b) ····: Potential scanned further negative in the presence of the urea. Scan rate = 100 mV/s.

Table 1. Shift in Half-Wave Potential, $\Delta E_{1/2}$, for Different *para*-Substituted Nitrobenzenes in the Presence of Diphenylurea[a]

substituent	$E_{1/2}$, V vs Fc	$\Delta E_{1/2}{}^{0/1-}$ (mV)
NH_2	−1.870	197
CH_3O	−1.698	164
CH_3	−1.635	156
H	−1.582	153
CF_3	−1.362	93

[a] 1 mM nitrobenzene in 0.10 M NBu_4PF_6/DMF + 50 mM 1,3-diphenylurea. Values are the average of at least three independent measurements.

If the potential is scanned further negative in the presence of the 1,3-diphenylurea (Figure 1b, ····), a new completely irreversible reduction process is observed. This leads to a decrease in the size of the NB^{1-} oxidation peak and the appearance of a new oxidation peak at more positive potentials. The amount of current in the irreversible reduction indicates that this is a multielectron process. It is likely caused by proton transfer to the radical anion, quite possibly facilitated by hydrogen bonding.

Similar behavior is observed with NB and 1,3-diphenylurea in DMF. The shift in $E_{1/2}$ for the $NB^{0/-1}$ wave in the presence of 1,3-diphenylurea is smaller than that in CH_2Cl_2, but still quite significant, +107 mV at 10 mM urea. Upon further addition of the urea (possible because of the greater solubility of diphenylurea in DMF than CH_2Cl_2), the $NB^{0/-1}$ wave continues to shift positive with no evidence of saturation up to a 200-fold excess. As in CH_2Cl_2, the NB reduction is chemically reversible if the potential is switched immediately after the reduction, but a second totally irreversible reduction is observed at more negative potentials.

Effect of $E_{1/2}$ on $\Delta E_{1/2}$. The simplicity of the nitrobenzene/urea system makes this a particular convenient one with which to explore the relationship between $E_{1/2}$ of a redox-dependent receptor and the magnitude of the potential shift, $\Delta E_{1/2}$. As shown in Table 1, by placing substituents of different donor/acceptor ability in the para position, the redox potential of nitrobenzene can be varied significantly without altering the steric environment of the nitro group. Five different nitrobenzene derivatives were examined, ranging from the trifluoromethyl derivative with an $E_{1/2}$ of −1.362 V vs Fc/Fc^+ to the amino derivative, nitroaniline, with an $E_{1/2}$ of −1.870 V vs Fc/Fc^+. The $\Delta E_{1/2}$ values were measured for these five compounds under identical experimental conditions, 50 mM 1,3-diphenylurea in DMF. The results, listed in Table 1, show that as $E_{1/2}$ becomes more negative, $\Delta E_{1/2}$ increases. Qualitatively, this seems reasonable because the nitrobenzenes with the more negative $E_{1/2}$'s will likely have more of the negative charge localized on the nitro oxygens in the reduced state. This should increase the strength of the hydrogen bond, resulting in a larger $\Delta E_{1/2}$. Further studies are planned to explore this relationship in a more quantitative fashion, but for the moment we note that this substituent effect provides a straightforward method to modulate the strength of the redox-dependent interaction.

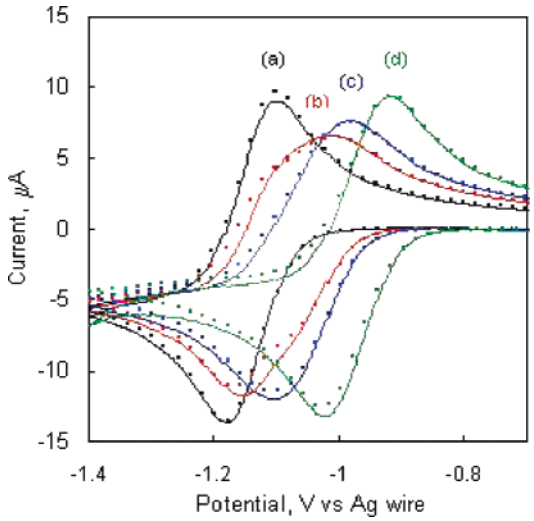


Figure 2. Experimental voltammograms (−) and simulated voltammograms (●) of 1 mM nitroaniline, NA, in DMF in the presence of increasing amounts of 1,3-diphenylurea: (a) 0 urea, (b) 0.5 mM urea, (c) 1 mM urea, (d) 10 mM urea. Scan rate = 500 mV/s.

Voltammetric Simulation. Nitroaniline, NA, was chosen for further study not only because it gave the largest $\Delta E_{1/2}$, but also because the electrochemistry appears more ideal than that of nitrobenzene as judged by the peak-to-peak separation, ΔE^p. As shown by Gokel, Echegoyen, and Kaifer a number of years ago,[21] the best way to obtain quantitative information on redox-dependent binding systems such as this is to use digital simulation methods to fit the experimental voltammograms. Accordingly, titration experiments were run in DMF in which voltammograms were recorded at several scan rates with incremental additions of 1,3-diphenylurea up to ~50 mM. The resulting data were then fit to the square scheme shown in Scheme 2 using commercially available software. The average results for the fitted parameters from three separate experiments are also given in Scheme 2.

Figure 2 shows representative experimental cyclic voltammograms (−) from one of the titrations overlaid with the best fit simulated voltammograms (●). There is some difficulty fitting the currents, particularly at the switching potential, due to a combination of background subtraction problems and the onset of the irreversible second reduction. However, in general the fit to the peak potentials and overall wave shape is good. Most notably, the simulations are able to reproduce both the changes in peak potentials with added urea and the observed broadening

(21) Miller, S. R.; Gustowski, D. A.; Chen, Z.; Gokel, G. W.; Echegoyen, L.; Kaifer, A. E. *Anal. Chem.* **1988**, *60*, 2021−2024.

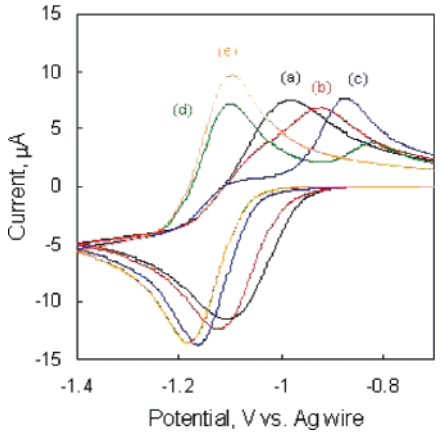


Figure 3. Simulated voltammograms showing the effect of decreasing $k_{f,ox}$ and $k_{f,red}$ on the voltammograms of 1 mM NA + 1 mM 1,3-diphenylurea. All parameters other than $k_{f,ox}$ and $k_{f,red}$ are the best fit values determined for the data shown in Figure 2. (a) $k_{f,ox} = 4.3 \times 10^{10}$ M^{-1} s^{-1} and $k_{f,red} = 3.7 \times 10^{8}$ M^{-1} s^{-1} (best fit to data), (b) $k_{f,ox} = 4.3 \times 10^{8}$ M^{-1} s^{-1} and $k_{f,red} = 3.7 \times 10^{6}$ M^{-1} s^{-1}, (c) $k_{f,ox} = 4.3 \times 10^{6}$ M^{-1} s^{-1} and $k_{f,red} = 3.7 \times 10^{4}$ M^{-1} s^{-1}, (d) $k_{f,ox} = 4.3 \times 10^{4}$ M^{-1} s^{-1} and $k_{f,red} = 3.7 \times 10^{2}$ M^{-1} s^{-1}, and (e) $k_{f,ox} = 4.3 \times 10^{2}$ M^{-1} s^{-1} and $k_{f,red} = 3.7$ M^{-1} s^{-1}.

of the voltammetric wave at low urea concentrations followed by sharpening at higher concentrations. The simulations indicate that these changes are due to a combination of very weak interaction between the urea and NA ($K_{ox} = 2.3 \times 10^{-3}$ M^{-1}), very strong interaction with NA^- ($K_{red} = 7.8 \times 10^{4}$ M^{-1}), and extremely fast rates for formation of the hydrogen-bonded complex (k_f's = 10^8–10^{10} M^{-1} s^{-1}).

The importance of rapid hydrogen-bonding equilibria is demonstrated more concretely in Figure 3, which shows the effect of decreasing forward rate constants for hydrogen bonding, $k_{f,ox}$ and $k_{f,red}$, on the voltammetry. CV (a) is the simulated voltammogram for 1 mM NA + 1 mM 1,3-diphenylurea (same as Figure 2c) using the best fit parameters determined for the data set shown in Figure 2. CV's (b–e) show simulated voltammograms using the same parameters as in (a) except for decreasing $k_{f,ox}$ and $k_{f,red}$.

The simulations show that as the rate constants decrease, the hydrogen-bonding equilibria become less effective in shifting the potentials. This initially causes the cathodic peak to move negative toward $E°$ for the NA/NA^- couple and the anodic peak to move positive toward $E°$ for the NA–urea/NA–$urea^-$ couple, creating an irreversible-looking CV wave, Figure 3b and c. This is the type of behavior observed by Leigh and co-workers for the molecular shuttle they constructed based on redox-dependent hydrogen bonding.[10e] In their system, the hydrogen-bonding equilibria are greatly slowed because the macrocyclic hydrogen donor must maneuver along a flexible chain to move on and off hydrogen acceptors located on either end of the chain. Still, the rate constants are fast enough that only one anodic peak is observed in their system. At even slower hydrogen-bonding rates, the simulations predict two anodic peaks, Figure 3d, because there will not be enough time for all of the NA^- to be complexed by urea at the scan rate used. At the slowest rates, Figure 3e, the complex will not be formed at all on the time scale of the CV and the voltammogram observed is just that of NA/NA^-.

Although manipulation of both the hydrogen-bonding rate constants and the heterogeneous electron-transfer rate constants, k_s,[22] is needed to obtain a good fit to the wave shape of the experimental voltammograms, the binding constant between NA^- and urea, K_{red}, is largely determined by the change in $E_{1/2}$ and is not very sensitive to changes in the rate constants.[23] This is good news, because given the number of parameters and the assumptions that need to be made to fit the experimental voltammograms, the values of the rate constants should be considered as approximations. The fact that K_{red} is not that sensitive to these values gives us confidence that we can determine K_{red} reliably from the simulations despite the uncertainty in the rate constants. On the other hand, the K_{ox} values are much more sensitive to the values of the rate constants. This means that it is not possible to determine K_{ox} accurately from these data, although it is clear that it must be small. In fact, completely removing the hydrogen-bonding equilibria between NA and urea from the reaction mechanism gives close to the same value for K_{red} and almost as good a fit to the experimental data.

The lack of significant hydrogen bonding between diphenylurea and the oxidized NA in DMF is confirmed by NMR titrations. Only insignificant changes in the urea N–H chemical shift are observed upon addition of up to 100-fold excess nitroaniline in d_7-DMF.[24]

Although there is no significant interaction between NA and diphenylurea, the electrochemical results clearly indicate very strong binding between NA^- and diphenylurea. As listed in Scheme 2, the average results from three separate titration experiments give a value of 7.8×10^4 M^{-1} for K_{red}. This is 80 times greater than that we previously measured with phenanthrenequinone and diphenylurea under the same experimental conditions. It is not possible to make a direct comparison with the other systems listed in Scheme 1 because the solvent systems are different. However, the K_{red} value for the NA/diphenylurea system in DMF is generally of the same order of magnitude or greater than those reported for the flavin and naphthalimide systems in CH_2Cl_2, a solvent which should give stronger hydrogen bonding. (An exception to this is the more elaborate

(22) The rapid rate of hydrogen bonding in the NA–urea system also has the interesting effect of making the CV's more sensitive to the electron-transfer rate constants, k_s. For a CV to be sensitive to k_s, the time scale must be such that equilibrium concentrations are not reached at the electrode surface. The scan rates that were used in this work are certainly not large, 200–1500 mV/s, and under normal circumstances a CV wave would not be sensitive to k_s values of the magnitudes reported at these scan rates. However, in the presence of urea, the rapid hydrogen bonding removes NA^- fast enough that equilibrium is not reached even at these relatively slow scan rates, thus making it possible to estimate k_s from these data. The results indicate that the electron-transfer rate to the NA–urea complex is about 10 times faster than that to NA itself. This can be rationalized by considering solvent reorganization energy, which has a large effect on electron-transfer rates according to Marcus theory. The more delocalized is the charge, the smaller is the solvent reorganization energy and the faster is the electron transfer. Hydrogen bonding to the radical anion should help to delocalize the charge, thereby decreasing the solvent reorganization energy and increasing the electron-transfer rate.

(23) For example, the best fit to the titration data shown in Figure 2 gives a K_{red} of 7.1×10^4 M^{-1}, with an electron-transfer rate constant, k_s, for NA/NA^- of 0.28 cm/s and a forward rate constant for formation of NA^-, $k_{f,red}$, of 5×10^8 M^{-1} s^{-1}. Varying k_s between 0.05 and 1×10^4 cm/s (with $k_{f,red} = 1 \times 10^9$ M^{-1} s^{-1}) changes the best fit K_{red} from 7.5×10^4 to 7.0×10^4 M^{-1}. In varying the $k_{f,red}$ from 1×10^7 to 1×10^{10} M^{-1} s^{-1}, the best fit K_{red} ranges between 7.16×10^4 and 7.24×10^4 M^{-1}.

(24) ^1H NMR experiments in d_7-DMF do show small upfield shifts in the urea NH peak upon addition of NA. However, these shifts, <0.1 ppm up to 100-fold excess, are very small as compared to those typically observed with NH hydrogen bonds; they are not reproducible, and they do not fit a 1:1 binding isotherm. Furthermore, we observe shifts of the same magnitude if we do a blank experiment by adding aliquots of d_7-DMF that do not contain NA. Therefore, the observed shifts do not indicate hydrogen bonding between the urea and NA. We believe they are most likely due to small amounts of water getting into the NMR tube as aliquots of the NA solution are added to the diphenylurea solution.

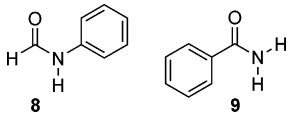
Table 2. Shift in Half-Wave Potentials, $\Delta E_{1/2}$, for Nitrobenzene, NB, and Nitroaniline, NA, in the Presence of Various NH- and OH-Containing Substrates[a]

substrate (50 mM)	$\Delta E_{1/2}$ $NB^{0/1-}$ (mV) CH_2Cl_2	$\Delta E_{1/2}$ $NB^{0/1-}$ (mV) DMF	$\Delta E_{1/2}$ $NA^{0/1-}$ (mV) DMF
water	27 ± 23	5 ± 4	9 ± 11
ethanol	7 ± 15	7 ± 6	5 ± 1
ethylene glycol	93 ± 113	31 ± 2	55 ± 8
propylamine	20 ± 16	5 ± 7	2 ± 3
ethylenediamine	18 ± 19	2 ± 11	3 ± 5
1,2-diaminobenzene	34 ± 16	10 ± 6	4 ± 5
benzamide	40 ± 39	4 ± 11	6 ± 5
formanilide	75 ± 9	23 ± 11	42 ± 12
butylurea	91 ± 14	24 ± 2	49 ± 11
1,3-dipropylurea	99 ± 29	33 ± 10	52 ± 5
1-phenyl-3-propylurea	209 ± 36	84 ± 6	130 ± 15
1,3-diphenylurea (10 mM in CH_2Cl_2)	188 ± 29	153 ± 15	197 ± 24
1,3-di-(4-trifluoromethylphenyl)urea	310 ± 87	205 ± 9	247 ± 11
1,1-dibutyl-3-phenylurea	1 ± 10	6 ± 3	3 ± 19

[a] 1 mM NB or NA in 0.10 M NBu_4PF_6/DMF or CH_2Cl_2 + 50 mM substrate. $\Delta E_{1/2}$ values are the average of at least three independent measurements. The ranges correspond to the 95% confidence limits.

azaflavin/guanidinium-melamine systems studied by Yano and co-workers, which show very strong binding even in the weaker binding oxidized state.[9d]) It is also worthwhile to note that, like the phenanthrenequinone/urea system, the nitrobenzene/urea system is distinguished from the others listed in Scheme 1 in that it represents a true on/off switch with significant binding observed in only one oxidation state. The other three systems all exhibit significant binding in both oxidation states.

Voltammetry of Nitrobenzene and Nitroaniline in the Presence of Other Substrates. Table 2 lists the shifts in $E_{1/2}$ observed for NB and NA in DMF in the presence of 50 mM of a variety of different OH- and NH-containing substrates. As with the previously studied *o*-quinones, no significant shifts are observed in DMF with water, ethanol, and all of the simple amino-containing substrates examined: propylamine, ethylenediamine, 1,2-diaminobenzene, and benzamide. With NB, small but significant shifts of 20−30 mV are observed for ethylene glycol, formanilide, butyl urea, and 1,3-dipropylurea. These same substrates give larger shifts of 40−55 mV with NA, consistent with the trend observed for diphenylurea in Table 1 and indicating generally stronger binding to the NA radical anion.



8 **9**

The above results suggest that significant binding to the nitrobenzene radical anions requires at least one hydrogen bond with a strong hydrogen donor like formanilide, **8**, which has an electron-withdrawing aryl group on the amide NH. In comparison, benzamide, **9**, with no electron-withdrawing group on the amide NH's, does not interact significantly with the radical anions. Alternatively, significant binding to the radical anion can be achieved with two hydrogen bonds to moderately strong hydrogen donors such as the two OH groups in ethylene glycol or the two nonaryl amide NH's in butylurea and 1,3-dipropylurea. As with the *o*-quinones, the largest shifts are observed with the diarylureas, which provide two hydrogens in strongly polarized bonds. Not surprisingly, addition of electron-withdrawing trifluoromethyl groups to the aryl rings leads to further polarization of the amide NH bonds and even larger shifts.

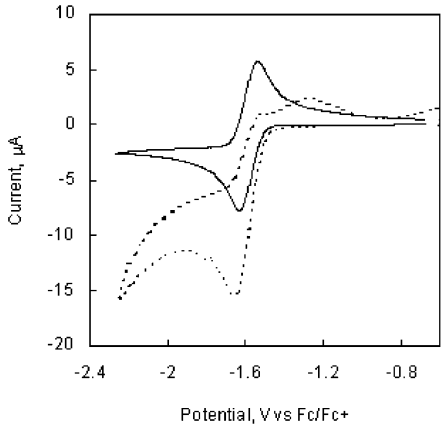


Figure 4. Cyclic voltammograms of 1 mM NB in CH_2Cl_2 by itself (−) and in the presence of 10 mM ethylacetoacetate (- - - -).

Proton Transfer versus Hydrogen Bonding. The fact that the current for nitrobenzene reduction does not increase upon addition of ureas is good evidence that the observed shifts are due to hydrogen bonding and not proton transfer. The latter would cause the reduction to shift to more positive potentials, but would also cause other distinctive changes in the voltammetry that are not observed. We confirmed this by examining the voltammetry of NB in DMF in the presence of a variety of organic compounds of different acidities.

Addition of 10 mM diethylmalonate ($pK_a = 16.4$ in DMSO[25]) and 10 mM dimethylmethylmalonate ($pK_a = 15.05$ in DMSO[25]) has no effect on the voltammetry of NB in DMF. In contrast, addition of the slightly more acidic ethylacetoacetate ($pK_a = 14.4$ in DMSO[25]) causes dramatic changes in the voltammetry as shown in Figure 4. As expected for proton transfer, the cathodic peak shifts positive and the current greatly increases. In addition, the return peak for NB^- oxidation disappears, and new, broad oxidation peaks appear at more positive potentials.

The above behavior is commonly seen with quinone radical anions in the presence of proton donors in aprotic solvents.[26] The increase in cathodic current is due to an ECE type mechanism. Initial one-electron transfer (the first "E" step) forms a radical anion. In the absence of any other reaction, additional electron transfer will occur only at more negative potentials because of the repulsive effect of the negative change. However, proton transfer to the radical anion (the "C" step) produces a neutral radical, which is typically easier to reduce than the original compound. This causes immediate transfer of a second electron (the second "E" step) leading to a doubling in current.

Clearly the voltammetry observed with the arylureas (Figures 1 and 2) is substantially different from that observed with a proton donor (Figure 4), so proton transfer is not a viable explanation for the large positive potential shifts observed for nitrobenzene derivatives in the presence of arylureas. This is also consistent with the pK_a values. The voltametric results with the different acids indicate that the pK_a of the protonated NB radical is between 14.4 and 15.0 on the DMSO scale. Because

(25) Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456−463.
(26) Eggins, B. R.; Chamber, J. Q. *J. Electrochem. Soc.* **1970**, *117*, 186−191.

the pK_a of 1,3-diphenylurea is 19.55 on this scale, it is much too weak of an acid to protonate the NB radical anion.

Conclusions

This work demonstrates a very strong, reversible, redox-dependent interaction between nitrobenzene derivatives and aryl ureas in aprotic solvents. There is essentially no interaction between these compounds in the oxidized state. However, reduction of nitrobenzene derivatives to their radical anions creates a very strong interaction with aryl ureas. Based on structural considerations and the reversibility of this interaction, we conclude this is due to a strong hydrogen bond formed between the nitro O's and the urea NH's. The result is a new, on/off organic redox switch that compares very favorably to those previously reported. In addition, the structural simplicity of the system makes it a particularly good model to explore other aspects of redox-dependent hydrogen bonding. For example, we were able to show that we could modulate the strength of the interaction not only by changing the structure of the non-redox active component, but also by changing the redox potential of the nitrobenzene. Finally, the synthetic ease with which nitro groups can be added to aromatic rings suggests that this system could be particularly useful for the creation of more elaborate receptors with greater selectivity and functionality.

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