Electrochemically-Controlled Hydrogen Bonding. Selective Recognition of Urea and Amide Derivatives by Simple Redox-Dependent Receptors

Yu Ge, Ronald R. Lilienthal, and Diane K. Smith*

Department of Chemistry, San Diego State University
San Diego, California 92182-1030

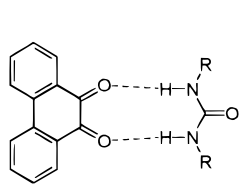
Received December 22, 1995

Hydrogen bonds, by virtue of their strength and directionality, are found extensively in biological systems controlling both intra- and intermolecular structure. In recent years chemists have begun to exploit hydrogen bonds for similar reasons. Indeed, receptors that utilize directed hydrogen bonds to bind substrates are of major importance in molecular recognition research.[1] Hydrogen bonds also are being used to build ordered, multimolecular assemblies in solution[2] and to engineer structures in the solid state.[3]

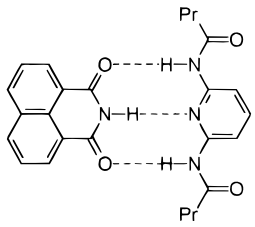
In this report we show how it is possible to control the strength of hydrogen bonding in a very straightforward manner using electrochemical means. Since hydrogen bonds are substantially electrostatic in nature,[4] a reduction or oxidation process that leads to a change in partial charge on one of the components in a hydrogen bond will have a significant effect on the strength of that hydrogen bond.

This, of course, is not a surprising or particularly novel observation. Certainly the effect of hydrogen bonds on redox potentials has been recognized,[5] particularly in the case of redox proteins.[6] It is known, for example, that the presence of hydrogen bonding to the flavin in flavoproteins will stabilize one redox state relative to the other, resulting in large shifts in the redox potential of the flavin.[7] What has not been recognized is the significance this has toward both molecular recognition and self-assembly in nonbiological systems. We demonstrate this here with two examples of redox-dependent receptors for amide and urea derivatives, which despite their simplicity show a high degree of selectivity.

The receptors are 9,10-phenanthrenequinone, **1**, and 1,8-naphthalimide, **2**. Both **1**[5] and **2**[8] undergo reversible one-electron reduction in aprotic media to form radical anions. Although the radical is delocalized, most of the negative charge will reside on the oxygens due to their greater electronegativity. For this reason, substrates with appropriately positioned N−H groups should hydrogen bond with the carbonyl oxygens much stronger in the reduced states. Examples of good substrates are urea derivatives with **1** and the diamidopyridine derivative **3** with **2**. These substrates should, in effect, stabilize the radical anions through hydrogen bonding, and this will cause the observed redox potential to shift positive. The maximum potential shift is related to the ratio of binding constants in the oxidized and reduced states (eq 1).[9]



1



2

3

$$\Delta E^{\circ}_{\max} = \frac{59mV}{n} \log\left(\frac{K_{red}}{K_{ox}}\right) \qquad (1)$$

The effect of hydrogen bonding on carbonyl reduction is nicely illustrated with 9,10-phenanthrenequinone, **1**, and 1,3-diphenylurea. As shown in structure **1**, and confirmed by molecular mechanics calculations, the N−H bonds in this urea are well-positioned to simultaneously hydrogen bond with both carbonyl oxygens in phenanthrenequinone. This leads to significant effects on the cyclic voltammetry (CV) of **1** as shown in Figure 1. Addition of 0.5 mM 1,3-diphenylurea to 1 mM **1** in CH_2Cl_2 leads to the appearance of an overlapping peak on the positive side of the CV wave (curve b). With 1 equiv of urea (curve c), one broad wave is observed which is shifted considerably positive of the original. The wave continues to shift positive with the addition of more urea until at 10 mM (curve d, close to the solubility limit) the wave is 207 mV positive of the original and the beginning of the second quinone reduction is evident at the negative end of the scan. From eq 1, the shift in redox potential corresponds to an increase in binding strength upon reduction by *at least* a factor of 3000.

The observation of overlapping waves at less than 1 equiv of guest in Figure 1 suggests diphenylurea also binds moderately well to the oxidized host.[9] However it is not possible to fit the observed voltammetry assuming only reversible electron transfer and binding. ^{1}H NMR indicates substantial aggregation of the urea in CH_2Cl_2,[10] and this is the likely cause of the nonideal behavior. To simplify the system we also looked at the voltammetry in DMF where the urea is not significantly aggregated. As shown in Figure 2 the observed shifts are much smaller than those in CH_2Cl_2, but they are still significant despite the highly competitive nature of the solvent. In this case we are able to fit the voltammetry assuming only reversible electron transfer and host−guest binding equilibria. The best fit corresponds to $K_{ox} = 1\ M^{-1}$ and $K_{red} = 660\ M^{-1}$.[11]

The effect of other N−H- and O−H-containing substrates on the redox potential of **1** is outlined in Table 1, which lists the observed change in half-wave potential, $\Delta E_{1/2}$, upon addition of 50 mM substrate. Like diphenylurea, butylurea and 1-phenyl-3-propylurea also cause substantial positive potential shifts in

(1) For reviews, see: (a) Rebek, J. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 245. (b) Hamilton, A. D.; Fan, E.; Van Arman, S.; Vicent, C.; Tellado, F. G.; Geib, S. J. *Supramol. Chem.* **1993**, *1*, 247. (c) Webb, T. H.; Wilcox, C. S. *Chem. Soc. Rev.* **1993**, 383.

(2) (a) Whitesides, G. M.; Simanek, E. E.; Mathias, J. P.; Seto, C. T.; Chin, D. N.; Mammen, M.; Gordon, D. M. *Acc. Chem. Res.* **1995**, *28*, 37. (b) Geib, S. J.; Vicent, C; Fan, E.; Hamilton, A. D. *Angew. Chem., Int. Ed. Engl.* **1993**, *105*, 80. (c) Kimizuka, N.; Kawasaki, T.; Hirata, K.; Kunitake, T. *J. Am. Chem. Soc.* **1995**, *117*, 6360. (d) Bergeron, R. J.; Yao, G. W.; Erdos, G. W.; Milstein, S.; Gao, F.; Weimar, W. R.; Phanstiel, O. *J. Am. Chem. Soc.* **1995**, *117*, 6658.

(3) For discussions of "crystal engineering" using hydrogen bonding, see: (a) Aakeroy, C. B.; Seddon, K. B. *Chem. Soc. Rev.* **1993**, 397. (b) MacDonald, J. C.; Whitesides, G. M. *Chem. Rev.* **1994**, *94*, 2383.

(4) Morokuma, H. *Acc. Chem. Res.* **1977**, *10*, 294.

(5) Peover, M. E. *J. Chem. Soc.* **1962**, 4540.

(6) (a) Huang, J.; Ostrander, R. L.; Rheingold, A. L.; Walters, M. A. *Inorg. Chem.* **1995**, *34*, 1090. (b) Goodin, D. B.; McRee, D. E. *Biochemistry* **1993**, *32*, 3313. (c) Caffrey, M. S.; Daldal, F.; Holden, H. M.; Cusanovich, M. A. *Biochemistry* **1991**, *30*, 4119. (d) O'Brien, P.; Sweigert, D. A. *Inorg. Chem.* **1985**, *24*, 1405.

(7) Breinlinger, E.; Niemz, A.; Rotello, V. M. *J. Am. Chem. Soc.* **1995**, *117*, 5379.

(8) Viehbeck, A.; Goldberg, M. J.; Kovac, C. A. *J. Electrochem. Soc.* **1990**, *137*, 1460.

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

(10) ^{1}H NMR spectra of diphenylurea show a strong concentration dependence even at 0.1 mM in CD_2Cl_2. Complicated aggregation is indicated since the NH protons shift upfield at low concentrations and downfield at higher concentrations.

(11) The voltammograms were simulated using Digisim, ver. 2.0. Binding constants were obtained by simultaneously fitting eight background-subtracted experimental voltammograms containing from 0 to 50 mM diphenylurea. Considerable error is expected in the K_{ox} value due to its small magnitude, which indicates very little interaction between the neutral quinone and urea in DMF. Simulations ranging from $K_{ox} = 0.1$ to $3\ M^{-1}$ (corresponding to $K_{red} = 640-700\ M^{-1}$) give almost identical voltammograms. However, larger K_{ox} values cause increasingly larger changes in the simulated voltammograms and a decreasing fit to the experimental voltammograms.

0002-7863/96/1518-3976$12.00/0

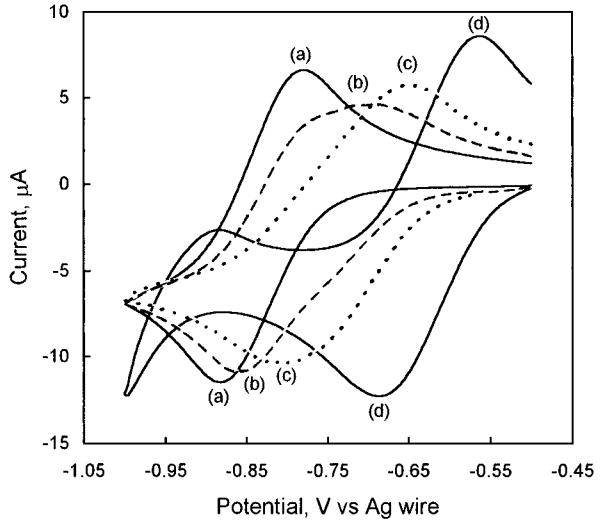


Figure 1. Cyclic voltammograms of 1 mM 9,10-phenanthrenequinone in 0.1 M NBu_4PF_6/CH_2Cl_2 in the presence of increasing amounts of 1,3-diphenylurea: (a) 0 mM urea, (b) 0.5 mM urea, (c) 1 mM urea, (d) 10 mM urea. Scan rate = 200 mV/s. A Ag wire in a separate compartment was used as the reference. Other conditions are the same as for the data in Table 1.

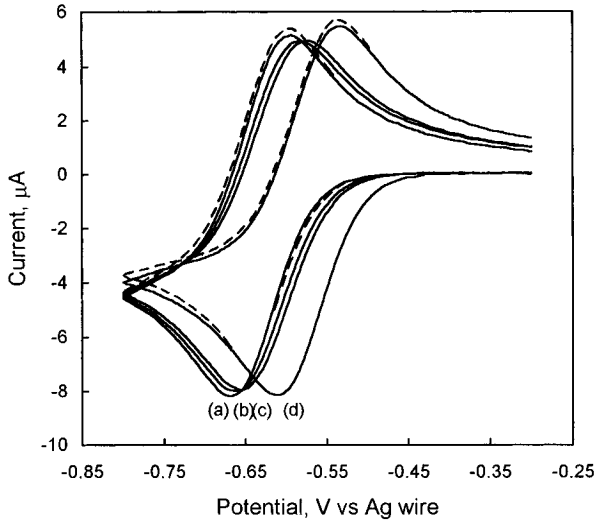


Figure 2. Cyclic voltammograms of 1 mM 9,10-phenanthrenequinone in 0.1 M NBu_4PF_6/DMF in the presence of increasing amounts of 1,3-diphenylurea: (a) 0 mM urea, (b) 0.5 mM urea, (c) 1 mM urea, (d) 10 mM urea. Dashed lines in curves (a) and (d) correspond to the theoretical voltammograms with $K_{ox} = 1.1\ M^{-1}$ and $K_{red} = 660\ M^{-1}$. Other conditions are the same as for the data in Figure 1.

CH_2Cl_2 and smaller but still significant shifts in DMF.[12] Note that 1,1′-dibutyl-3-phenylurea, which only has one N−H bond, produces a negligible shift in both solvents, indicating that hydrogen bonding to both carbonyls is essential. Water, ethanol, and propylamine also produce relatively small shifts, as well as the diaminoaromatic derivatives. In the latter, the N−H bonds are either too close together (1,2-diaminobenzene) or too far apart (1,3-diaminobenzene and 2,6-diaminopyridine) to simultaneously interact with both carbonyl oxygens. With all these substrates, including the ureas, the CV wave remains reversible, indicating that proton transfer does not occur. In contrast, addition of 1 equiv of phthalimide, which is fairly acidic, leads to irreversible electrochemistry.[13]

1,8-Naphthalimide, **2**, provides another example of redox-dependent binding achieved through H-bond perturbation. As shown in Table 1, we also observe large positive shifts in the half-wave potential of **2** in both CH_2Cl_2 and DMF in the presence of substrates which can form at least two H-bonds with the imide. The largest potential shifts are observed with the diamidopyridine derivative, **3**, which can bind through three H-bonds.[14] Smaller but still significant shifts are observed with 2,6-diaminopyridine. As with **1**, the CV wave of **2** generally remains reversible upon addition of substrate, indicating that proton transfer does not occur. The one exception is with propylamine where proton transfer likely does occur between the acidic imide H and the basic amine.

Table 1. Shifts in Half-Wave Potentials of Phenanthrenequinone, **1**, and Naphthalimide, **2**, in the Presence of Various N−H- and O−H-Containing Substrates[a]

	$\Delta E_{1/2}$ **1**$^{0/1-}$ (mV)		$\Delta E_{1/2}$ **2**$^{0/1-}$ (mV)	
substrate (50 mM)	CH_2Cl_2	DMF	CH_2Cl_2	DMF
water	+14		−2	
ethanol	+8		+12	
propylamine	0		irr[b]	
1,2-diaminobenzene	+11		+12	
1,3-diaminobenzene	+6		+28	
2,6-diaminopyridine	+7		+57	+27
3, R = propyl	+14		+128	+62
butylurea	+74	+24	+18	
1-phenyl-3-propylurea	+160	+73	+50	0
1,3-diphenylurea (10 mM)	+207	+59	+39	0
1,3-diphenylurea (50 mM)		+96		−5
1,1′-dibutyl-3-phenylurea	+6	+5	+1	

[a] Change in $E_{1/2}$ upon addition of 50 mM substrate to 1 mM **1** or **2** in 0.1 M NBu_4PF_6/CH_2Cl_2 or DMF. Measured by cyclic voltammetry (CV). Other conditions: 2 mm Pt or Au disk electrode, Ag wire reference with ferrocene, cobaltocenium or *N,N,N′,N′*-tetramethylphenylenediamine used as an internal potential reference, 100 or 50 mV/s scan rate, 22 °C. [b] CV wave becomes irreversible.

In conclusion, we have shown that 9,10-phenanthrenequinone and 1,8-naphthalimide are redox-dependent receptors for urea and amide derivatives with appropriately positioned N−H bonds. The observed potential shifts, similar to those measured in a flavoprotein model system,[7] are by far the largest reported to date for purely organic receptor/substrate systems.[15−17] Clearly H-bond perturbation is a powerful technique for achieving redox dependence in such systems. It is also noteworthy that reduction can transform a rather poor receptor into a good receptor. This has implications not only for molecular recognition but also for self-assembly. In particular, it suggests electron transfer could be used to trigger the assembly, disassembly, or rearrangement of H-bonded networks in solution.

Acknowledgment. We thank Gregg Lane for providing some of the urea derivatives and Stephanie Shaw for synthesizing **3**. We also thank San Diego State University Foundation and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for financial support of this work.

JA954283K

(12) The strong binding of **1** to the disubstituted ureas, particularly diphenylurea, may also be partly due to preorganization of these compounds for binding. AM1 semiempirical molecular orbital calculations indicate that the "cis" conformation necessary for binding, with both N−H's pointing away from the carbonyl, is a low-energy conformation.

(13) Since the basicity of the receptor will increase upon reduction, it is likely that there has to be a large difference in pK_a's between the neutral receptor and the substrate to prevent proton transfer. Amides are particularly good in this regard since they are good H donors without being very acidic.

(14) **3** and related compounds have been shown to form triple H-bonded complexes with the imide functional group in other compounds. Feibush, B.; Figueroa, A.; Charles, R.; Onan, K. D.; Feibush, P.; Karger, B. L. *J. Am. Chem. Soc.* **1986**, *108*, 3310. See also ref 7.

(15) There are actually very few examples of purely organic, synthetic, redox-dependent receptor/substrate systems. See ref 16. To the best of our knowledge, the only other reported example of an organic receptor/substrate system where binding strength changes significantly with oxidation state is a viologen-based receptor that has been studied by us and others (ref 17).

(16) Beer, P. D. *Adv. Inorg. Chem.* **1992**, *39*, 79.

(17) (a) Lilienthal, R. R.; Smith, D. K. *Anal. Chem.* **1995**, *67*, 3733. (b) Smith, E. A.; Lilienthal, R. R.; Fonseca, R. J.; Smith, D. K. *Anal. Chem.* **1994**, *66*, 3013. (c) Bernardo, A. R.; Stoddart, J. F.; Kaifer, A. E. *J. Am. Chem. Soc.* **1992**, *114*, 10624.