

Electrochemically Controlled Hydrogen Bonding. Electrolyte Effects in an Oxidation-Based Arylurea–Amide System

Jessica E. Woods, Yu Ge, and Diane K. Smith*

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

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Over the past decade, it has been shown that it is possible to selectively and significantly perturb the strength of H-bonding between organic molecules using electrochemistry. However, although both reduction¹ and oxidation² reactions have been used, reductions have generally proven more successful.³ In this paper, we show that the difficulty with oxidations can be due to an electrolyte effect resulting from competition between the guest and the electrolyte anion for H-bonding to the oxidized host. Furthermore, we show that, by switching to an electrolyte with a very large anion, significant changes in binding strength are observed upon oxidation of an electroactive urea in the presence of a diamide guest.

The basic idea behind redox-dependent hydrogen bonding is to use the change in charge accompanying e-transfer to perturb the strength of H-bonds between host and guest. One possibility is to use a reduction reaction to increase negative charge on H-accepting atoms in a host. Another possibility, which is explored in this study, is to use an oxidation reaction to increase the positive charge on H-donating groups in the host. H-accepting guests will then bind more strongly to the oxidized form, making it easier to oxidize the host. This results in a negative shift in the half-wave potential, $E_{1/2}$, of the host in the presence of the guest.

Since the perturbation of H-bond strength relies on a change in charge, ion–ion interactions may also play a role in these systems. They can be used to advantage when the guest itself is ionic,⁴ but with neutral guests, they may pose a problem. This is particularly an issue in electrochemical studies, where an “inert” electrolyte will be present in excess. The most common electrolytes used in these studies are NBu_4ClO_4 or NBu_4PF_6 .² Use of NBu_4^+ is a good choice for reduction-based systems because it is a very large ion and is unlikely to significantly ion pair in the solvents commonly used for these studies.⁵ However, the same cannot be said about ClO_4^- or PF_6^- . This has been particularly noted by Geiger in electrochemical studies of organometallic cations.⁶

In this work, we show that interaction with ClO_4^- or PF_6^- can also be an issue for oxidation-based, redox-dependent H-bonding. The system under investigation is based on the urea, **U**. This compound was chosen because diarylureas are known to be very good H-donors, and oxidation of the NMe_2 -phenyl ring should lead to a significant increase in positive charge on one of the urea NH's (eq 1). For comparison purposes, we also synthesized the methylated derivative, **UMe**.

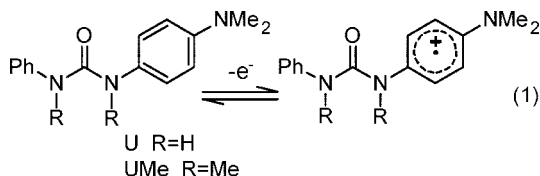


Figure 1 shows cyclic voltammograms (CVs) of **U** in CH_2Cl_2 with (a) NBu_4ClO_4 , (b) NBu_4PF_6 , and (c) $\text{NBu}_4\text{B}(\text{C}_6\text{F}_5)_4$ as the

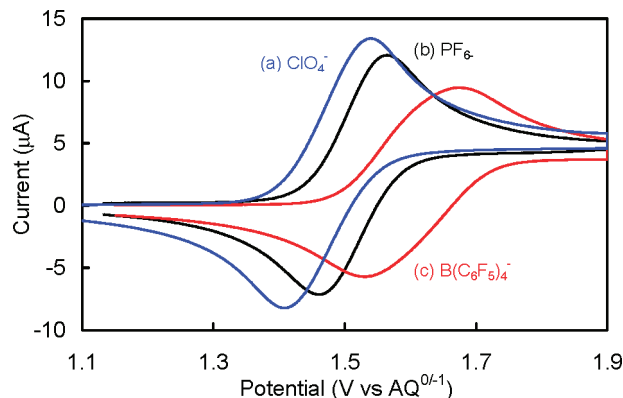
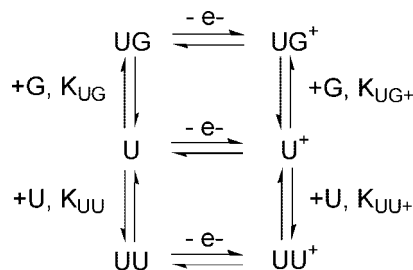


Figure 1. CVs (100 mV/s) of 1 mM **U** in CH_2Cl_2 with (a) 0.1 M NBu_4ClO_4 , (b) 0.1 M NBu_4PF_6 , and (c) 0.1 M $\text{NBu}_4\text{B}(\text{C}_6\text{F}_5)_4$.

Scheme 1. Mechanism for **U** Oxidation with Guest, **G**, Present



electrolyte. Clearly, the electrolyte anion has a big effect on the electrochemistry. With ClO_4^- , reversible oxidation to the radical cation, U^{0+} , is observed at 1.47 V, with PF_6^- , the same process occurs at 1.51 V, and with $\text{B}(\text{C}_6\text{F}_5)_4^-$, it is at 1.60 V. In addition, the U^{0+} wave is considerably broader with $\text{B}(\text{C}_6\text{F}_5)_4^-$ than ClO_4^- or PF_6^- . Close inspection of the U^{0+} wave in Figure 1c suggests that it actually represents two strongly overlapping waves of equal height. Interestingly, when the same set of CVs is run with **UMe**, the $E_{1/2}$ values are much closer (within 0.03 V) and there is no significant difference in wave shape between the three electrolytes.⁷ This strongly suggests that it is an ionic H-bonding interaction between the anions and the urea NH's that is mainly responsible for the differences between electrolytes seen in Figure 1.

A mechanism capable of explaining the differences observed in Figure 1 is given in Scheme 1. If a guest, **G**, is present that binds more strongly to U^+ than **U**, the observed $E_{1/2}$ of U^{0+} will shift negative in the presence of **G**. This is what appears to happen in Figure 1a and b, with ClO_4^- or PF_6^- playing the role of **G** through strong interaction with the urea NH's. In contrast, if no **G** is present, as with $\text{B}(\text{C}_6\text{F}_5)_4^-$, then U^+ could interact with **U** to form the UU^+ dimer shown below. Since **U** would bind more strongly to U^+ than another **U**, the $E_{1/2}$ shifts negative as UU^+ is being formed. This continues until half of the **U** is oxidized to U^+ . Oxidation of the

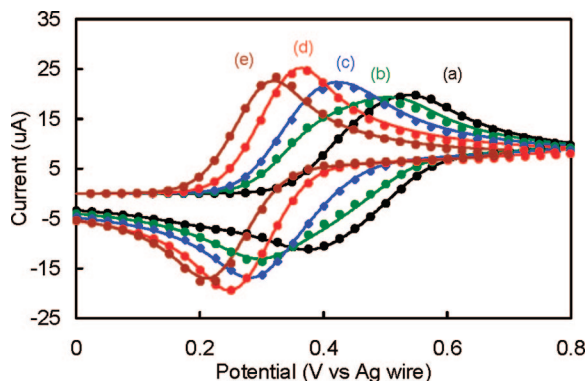
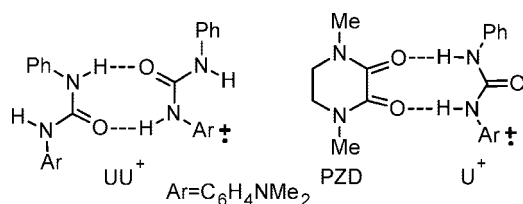


Figure 2. Experimental (solid lines) and simulated (dots) CVs (500 mV/s) of 1 mM U in 0.1 M NBu₄B(C₆F₅)₄/CH₂Cl₂ + PZD: (a) 0 mM, (b) 0.5 mM, (c) 1 mM, (d) 5 mM, (e) 100 mM.

rest of U then occurs upon dissociation of UU⁺. This would occur at a slightly more positive potential, producing the broad wave observed for U^{0/+} with B(C₆F₅)₄[−].



The occurrence of U dimerization in CH₂Cl₂ is supported by ¹H NMR data for U in CD₂Cl₂ that show the NH chemical shifts are concentration-dependent. Analysis of these data gives $K_{UU} = 22 \text{ M}^{-1}$. Using this value, CVs of 0.5 and 1 mM U in NBu₄B(C₆F₅)₄/CH₂Cl₂ were fit to a slightly modified version⁷ of the mechanism shown in Scheme 1, giving $K_{UU+} = 4600 \text{ M}^{-1}$.

The fact that U⁺ binds so strongly to another U suggests there must be other molecular guests that will strongly bind to U⁺ and produce large shifts in the observed $E_{1/2}$ of U^{0/+}. Past experience^{1c,d} suggests that this requires a guest with two strong H-acceptor atoms preorganized to H-bond with both urea NH's. 1,4-Dimethylpiperazine-2,3-dione, abbreviated PZD, nicely satisfies these criteria as shown above.

It turns out that PZD is a good enough guest for U that large $E_{1/2}$ shifts are observed in all electrolytes. The difference is how much PZD needs to be added. With ClO₄[−] or PF₆[−], addition of 1 mM PZD to 1 mM U in CH₂Cl₂ produces a −2 or −16 mV shift, respectively, in the $E_{1/2}$ of U^{0/+}, with little change in the shape or size of the CV wave.⁷ As more PZD is added, the wave shifts further negative. By 400 mM PZD, the shift is significant, −60 mV with ClO₄[−] and −114 mV with PF₆[−], but there is no evidence that the maximum shift is nearing.

Figure 2 shows experimental and simulated CVs for the same type of experiment done with NBu₄B(C₆F₅)₄. Now addition of 1 mM PZD causes a −109 mV shift, almost as large as that observed with 400 mM in PF₆[−]. Along with the shift, there is a substantial sharpening of the wave, indicating that PZD binding is competing

successfully with U dimerization. By 5 mM PZD, the wave has reached full height, and by 100 mM, the system appears to be closing in on a maximum shift of about −200 mV. This corresponds to a >2000-fold increase in binding strength upon oxidation. To the best of our knowledge, this is by far the largest binding enhancement reported to date for an oxidation-based, redox-dependent H-bonding system with a neutral molecular guest. From the simulated CVs, we obtain reliable estimates of the actual binding constants in the two oxidation states: $K_{UG} = 62 \text{ M}^{-1}$ and $K_{UG+} = 1.6 \times 10^5 \text{ M}^{-1}$.

In conclusion, we have demonstrated a simple redox-dependent H-bonding system in which oxidation leads to a substantial increase in binding strength to a molecular guest. Indeed, the magnitude of the effect is comparable to that observed for the better reduction-based systems. However, it is doubtful that this system is unique. The difference is the electrolyte. Binding to the commonly used electrolyte anions ClO₄[−] and PF₆[−] is strong enough to obscure the strength of binding to the guest. It is likely that other oxidation-based systems would also reveal much stronger binding if re-examined using less competitive electrolytes.

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Supporting Information Available: Additional CVs, NMR titration data and analysis, general voltammetry and CV simulation procedures, synthesis and structural data for UMe. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (3) There are a number of examples (see ref 1) where perturbation of H bonds through reduction results in a > 10-fold change in binding strength between an electroactive host and a neutral guest. In contrast, to our knowledge, the ferrocene diamides studied by Green, Tucker, and colleagues (ref 2e) remain, until now, the only reported examples where oxidation does the same.
- (4) Much greater success has been achieved with oxidation-based H-bonding receptors for anions. For a recent example, see Willener, Y.; Joly, K. M.; Moody, C. J.; Tucker, J. H. R. *J. Org. Chem.* **2008**, *73*, 1225–1233.
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- (7) See Supporting Information.

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