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Synthesis of a Redox-Responsive Quadruple Hydrogen-Bonding Unit for Applications in Supramolecular Chemistry

Ying Li, Taiho Park,[†] J. Kwansima Quansah, and Steven C. Zimmerman*

Department of Chemistry, University of Illinois, 600 South Mathews Avenue, Urbana, Illinois 61801, United States

Supporting Information

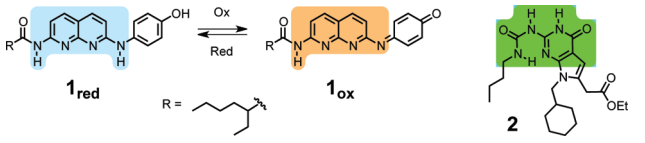
ABSTRACT: A redox-responsive quadruple hydrogen-bonding module (eDAN) has been developed. The strong binding between the reduced form and its partner (DeUG) can be significantly decreased upon oxidation but restored upon subsequent reduction. This on−off switch was successfully applied to provide reversible control of macroscopic supramolecular polymer networks.

Supramolecular building blocks featuring arrays of hydrogen-bond donor and acceptor groups have played a key role in self-assembled systems, nanofabrication, and supramolecular polymer chemistry.[1] One advantage of the supramolecular approach is that it allows for the development of stimuli-responsive or smart systems and devices. For example, the hydrogen-bond complexation strength is quite sensitive to pH, temperature, and solvent polarity.[2] Indeed, Leigh and co-workers showed that protonation of 2,6-diaminopyridine, a unit with a DAD hydrogen-bonding array (D = donor, A = acceptor) converts it into a DDD unit, thereby increasing its affinity for an AAA unit by >10^9-fold.[3] Smith recently defined a good switch as one in which the external signal changes the association constant (K_{assoc}) by at least 10-fold.[4] By this measure, the Leigh system is remarkable, equivalent to an on−off switch. Furthermore, it points to the general utility of altering the hydrogen-bonding motif in developing effective stimuli-responsive units. However, external stimuli such as pH, temperature, and solvent polarity changes often lack the necessary selectivity when more than one hydrogen-bonded complex is involved, and switching can prove difficult to achieve in a practical setting.

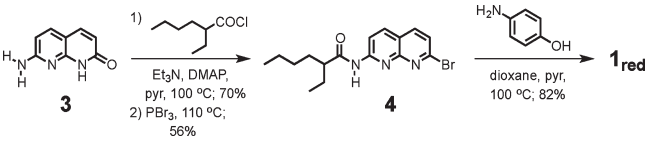
Photo- and electrochemical approaches have some distinct advantages because often they are reversible and efficient, avoiding the addition of chemical reagents. Apart from Hecht's photoswitchable triple hydrogen-bonding motif,[5] considerable effort has focused on electroactive units.[4,6] Rotello[7] has pioneered a particularly useful redox approach involving the reduction of recognition units with imide-like groups. The reduction does not alter the hydrogen-bonding motif but rather converts the ADA array of hydrogen-bond donor and acceptor groups into the corresponding radical anion ($ADA^{\bullet-}$), which pairs more strongly with its complementary (DAD) partner.

Herein we report an approach that uses a redox reaction to transform the DAAD hydrogen-bonding array in $\mathbf{1}_{red}$ to a DAA (or DAAA) array in $\mathbf{1}_{ox}$, which leads to a surprisingly large change in hydrogen-bonding complexation strength (Scheme 1).

Scheme 1. Interconversion of $\mathbf{1}_{red}$ and $\mathbf{1}_{ox}$ and the Structure of 2



Scheme 2. Synthesis of $\mathbf{1}_{red}$



Compound **1** ($\mathbf{1}_{red}$ or $\mathbf{1}_{ox}$), designated as eDAN, is based on our previously reported 2,7-diamido-1,8-naphthyridine (DAN) unit that forms a very stable[8] and high-fidelity[9] quadruply hydrogen-bonded complex with the ureas of guanosine (UG)[10] and deazaguanosine **2** (DeUG).[11] The DeUG unit is a more stable and preparatively scalable analogue of UG. We further report that the eDAN redox switch can be applied to supramolecular hydrogen-bonded polymer blends.[12]

The three-step synthesis of $\mathbf{1}_{red}$ from commercially available **3** is outlined in Scheme 2. Compound **4** was recently reported as a substrate for copper-catalyzed amination.[13] However, neither Cu_2O nor various palladium catalysts effected the C−N bond formation between **4** and 4-aminophenol. Ultimately it was found that this amination reaction takes place directly using pyridine in dioxane at high temperature.[14]

The interconversion of $\mathbf{1}_{red}$ and $\mathbf{1}_{ox}$ was examined both chemically and electrochemically. Cyclic voltammetry indicated that the oxidation of **1** was not fully reversible [see the Supporting Information (SI)]. The redox half-reactions could be accomplished chemically and on a preparative scale by treatment of $\mathbf{1}_{red}$ with activated MnO_2.[15] The reduction back to $\mathbf{1}_{red}$ occurred with zinc/acetic acid (Zn/H^+).[16] With an eye toward applications and specifically an interest in materials that might respond to oxygen, a broader set of redox reagents were examined. As shown in Table 1, copper(II) acetate and *N*,*N*′-bis(salicylidene)ethylenediaminocobalt(II) (salcomine)[17] serve as catalysts for the O_2

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Table 1. Redox Chemistry of 1[a]

$$\mathbf{1}_{red} \underset{Red}{\overset{Ox}{\rightleftharpoons}} \mathbf{1}_{ox}$$

entry	redox agent	equiv	temp. (°C)	time (min)	yield (%)[b]
Ox-1	activated MnO_2	5	25	30	89
Ox-2	$Cu(OAc)_2/O_2$	0.2	50	720	82
Ox-3	salcomine/O_2	0.05	25	30	92
Red-1	Zn/H^+	2/20	25	30	80
Red-2	hydroquinone	1	25	30	96

[a] Reactions were performed in chloroform. [b] Isolated yields.

oxidation of $\mathbf{1}_{red}$. However, in the presence of **2**, only salcomine effected the conversion of $\mathbf{1}_{red}$ to $\mathbf{1}_{ox}$, with 0.1 equiv required to reach ca. 80% conversion. The resistance to oxidation in the presence of **2** can be attributed to the high stability of the $\mathbf{1}_{red}\cdot\mathbf{2}$ complex and the low solubility of $Cu(OAc)_2$ in chloroform. The reduction of $\mathbf{1}_{ox}$ was effected by hydroquinone in 96% yield.

The abilities of $\mathbf{1}_{red}$ and $\mathbf{1}_{ox}$ to complex **2** were examined qualitatively by ^{1}H NMR spectroscopy (Figure 1). For the sake of clarity, CD_2Cl_2 was chosen as the NMR solvent. Worthy of note are the significant downshifts of the NH_A and NH_B protons of **2** upon addition of $\mathbf{1}_{red}$. In contrast, the same protons shift minimally upon addition of $\mathbf{1}_{ox}$. Quantitative complexation studies were performed with **1** and **2** in chloroform using isothermal titration calorimetry (ITC) (Figure 2). The $\mathbf{1}_{red}\cdot\mathbf{2}$ complex exhibited an apparent association constant (K_{assoc}) of 1.1×10^6 M^{-1}. After correction for the weak dimerization of **2**, which causes the endothermal dip leading up to 1 equiv in the ITC curve, the actual value of K_{assoc} was found to be 1.4×10^6 M^{-1}.[11,14] Although the ITC data for $\mathbf{1}_{ox}\cdot\mathbf{2}$ did not allow the binding to be quantified, a ^{1}H NMR titration study afforded a corrected K_{assoc} of 6.7×10^2 M^{-1} for $\mathbf{1}_{ox}\cdot\mathbf{2}$. The large value of K_{assoc} for $\mathbf{1}_{red}\cdot\mathbf{2}$ is similar to that reported for the DAN·UG and DAN·DeUG complexes.

The more than 2×10^3-fold decrease in K_{assoc} represents one of the largest attenuations of binding strength for a redox switch. Indeed, the nearly 5 kcal mol^{-1} loss of binding affinity is too large to be attributed to the loss of a single hydrogen bond. Similar DAA·ADD complexes show K_{assoc} values of ca. 10^4 M^{-1}.[8] Two factors may readily account for the weaker binding by $\mathbf{1}_{ox}$. First, simple modeling indicates that $\mathbf{1}_{ox}$ prefers the conformer shown in Figure 2b, in which the azaquinone unit sterically blocks the DAA hydrogen-bonding edge. The complexation may occur as shown in the $\mathbf{1}_{ox}\cdot\mathbf{2}$ complex in Figure 1b (DAAA array), but it contains two flanking nonbonded electron pairs (a destabilizing interaction) and uses a less stable conformer.

We previously reported that polystyrene (PS) and poly(butyl methacrylate) (PBMA), two ordinarily immiscible polymers, form miscible blends/gels when the PS and PBMA contain DAN and UG units, respectively, at compositions of a few mole percent.[12] The ability of free DAN to inhibit this supramolecular polymer blend suggested the use of eDAN **1** to create stimuli-responsive systems. PS-DAN (**5**) was synthesized in three steps, including a free radical polymerization as described previously, except with the small but significant change that the synthesis began with 2-ethylhexylamido-containing DAN **4** (Scheme 3a). In comparison with the previous approach,[12] the incorporation of the branched alkyl chain greatly improved the

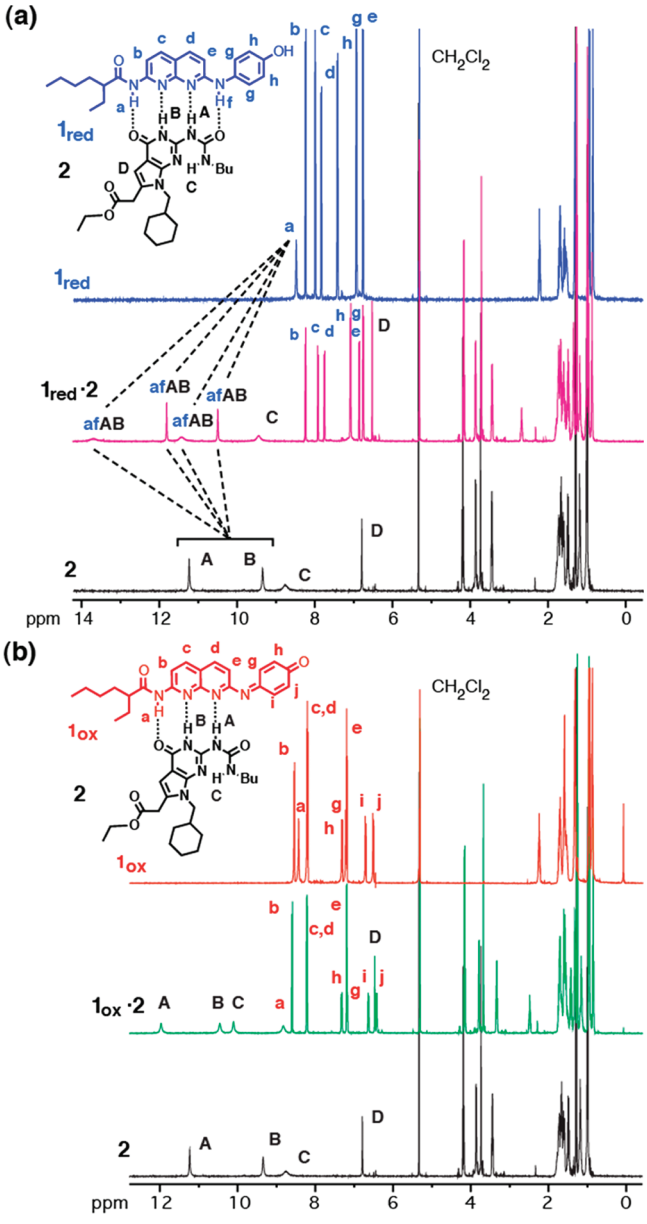

Figure 1. (a) ^{1}H NMR spectra (500 MHz, CD_2Cl_2, 295 K) of (top) $\mathbf{1}_{red}$, (middle) $\mathbf{1}_{red}\cdot\mathbf{2}$, and (bottom) **2** showing the changes to $\mathbf{1}_{red}$ and **2** upon association to form $\mathbf{1}_{red}\cdot\mathbf{2}$. (b) ^{1}H NMR spectra (500 MHz, CD_2Cl_2, 295 K) of (top) $\mathbf{1}_{ox}$, (middle) $\mathbf{1}_{ox}\cdot\mathbf{2}$, and (bottom) **2**. The assignments in (a) and (b) are tentative. The $\mathbf{1}_{red}\cdot\mathbf{2}$ complex may form two ways, both likely in fast exchange. Some peaks are cut off.

yield, of each step in Scheme 3 perhaps because of its increased resistance to cleavage and improved solubility.[18]

PBMA-DeUG (**6**) was synthesized analogously to the previously described[12] UG-containing PBMA (Scheme 3b). Shorter linkages between the DeUG unit and the polymer backbone were examined but led to opaque, viscous polymer solutions upon mixing with PS-DAN **5** in chloroform, indicating phase separation. Both of the polymers were characterized by size-exclusion chromatography (SEC) and ^{1}H NMR spectroscopy, the latter indicating that the degrees of recognition-unit incorporation were 6 and 4 mol % for **5** and **6**, respectively. The SEC instrument was equipped with a UV detector, which confirmed the attachment of DAN and DeUG and gave the following polymer

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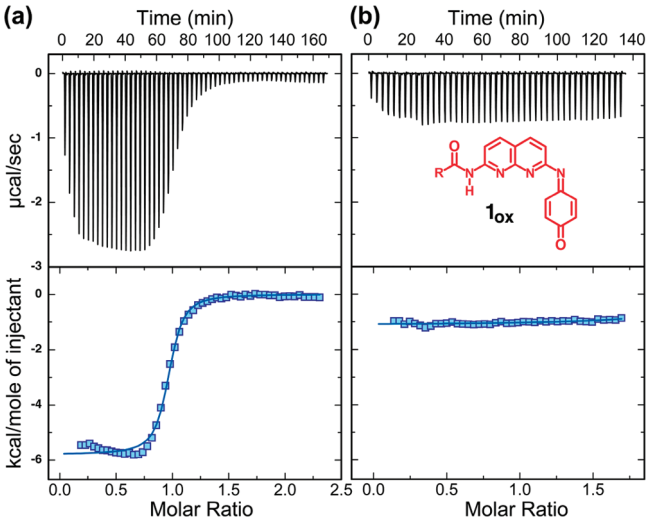
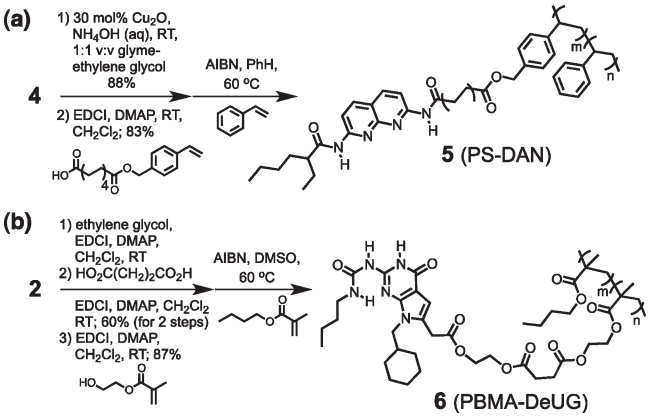


Figure 2. ITC data for (a) $\mathbf{1}_{red}\cdot\mathbf{2}$ and (b) $\mathbf{1}_{ox}\cdot\mathbf{2}$. A detailed discussion of the ITC data can be found in the SI.

Scheme 3. Synthesis of Reactive Monomers and Copolymerization To Give (a) PS-DAN (5) and (b) PBMA-DeUG (6)[a]



[a] Abbreviations: AIBN, azobis(isobutyronitrile); DMAP, 2,6-dimethylaminopyridine; EDCI, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide.

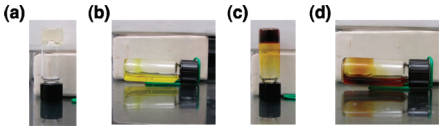


Figure 3. [14](a) Blend of PS-DAN and PBMA-DeUG. (b) Blend with $\mathbf{1}_{red}$ added. (c) Reformation of viscous gel by oxidation of $\mathbf{1}_{red}$ to $\mathbf{1}_{ox}$. (d) Redestruction of the polymer blend by reduction of $\mathbf{1}_{ox}$ to $\mathbf{1}_{red}$.

information: PS-DAN (**5**) M_n = 18.5 kDa, PDI = 1.41; PBMA-DeUG (**6**) M_n = 24 kDa, PDI = 1.23. Details of the polymer synthesis and characterization can be found in the SI.

Switching experiments were performed by dissolving PS-DAN **5** and PBMA-DeUG **6** in chloroform at a concentration of 30 g/dL. Upon addition of the solution of **6**, the clear, free-flowing solution of **5** became a viscous gel (Figure 3a). Upon addition of $\mathbf{1}_{red}$ (ca. 100 equiv per DeUG unit), the gel was destroyed (Figure 3b). After treatment with salcomine (<0.5 equiv with respect to $\mathbf{1}_{red}$) and bubbling of O_2 through the solution for 5 min, the gel was restored (Figure 3c). Finally, the reformed gel was treated with hydroquinone (1 equiv per eDAN **1**), leading to a solution (Figure 3d). Each step was followed by ^{1}H NMR spectroscopy, and control experiments were performed to confirm that the redox reagents were responsible for the $\mathbf{1}_{red}$ to $\mathbf{1}_{ox}$ interconversion and that this in turn controlled the formation of the supramolecular polymer blend.[14] Multiple cycles were not examined, but in ^{1}H NMR experiments with **1** alone, several redox cycles were possible, although obvious byproducts were formed.[14]

In conclusion, the redox-responsive eDAN module **1** was designed and shown to pair with high affinity to DeUG in its reduced form ($-\Delta G^\circ$ = 8.3 kcal mol^{-1} for $\mathbf{1}_{red}\cdot\mathbf{2}$) but to bind weakly when oxidized ($-\Delta G^\circ$ = 3.8 kcal mol^{-1} for $\mathbf{1}_{ox}\cdot\mathbf{2}$). The very large decrease in binding points to the utility of coupling the stimulus and the hydrogen-bonding motif displayed by the recognition unit. A simple application to stimuli-responsive supramolecular polymer networks that did not require incorporation of the responsive unit into the polymers was demonstrated. Future improvements will involve altering the naphthyridine unit in a way that allows reversible electrochemical switching.

■ ASSOCIATED CONTENT

Supporting Information. Synthetic procedures and characterization data, ^{1}H NMR and UV−vis titration studies, and ITC data. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author
sczimmer@illinois.edu

Present Addresses
[†]Department of Chemical Engineering, POSTECH, Pohang 790-784, Korea.

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