

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

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S Supporting Information

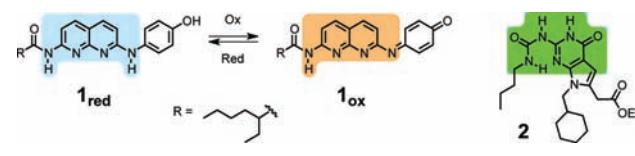
ABSTRACT: A redox-responsive quadruple hydrogen-bonding module (eDAN) has been developed. The strong binding between the reduced form and its partner (DeUG) can be significantly decreased upon oxidation but restored upon subsequent reduction. This on–off switch was successfully applied to provide reversible 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 >10⁹-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.

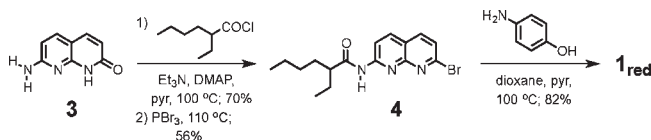
Photo- and electrochemical approaches have some distinct advantages because often they are reversible and efficient, avoiding the addition of chemical reagents. Apart from Hecht's photo-switchable triple hydrogen-bonding motif,⁵ considerable effort has focused on electroactive units.^{4,6} Rotello⁷ has 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^{•-}), 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 **1_{red}** to a DAA (or DAAA) array in **1_{ox}** which leads to a surprisingly large change in hydrogen-bonding complexation strength (Scheme 1).

Scheme 1. Interconversion of **1_{red}** and **1_{ox}** and the Structure of **2**



Scheme 2. Synthesis of **1_{red}**



Compound **1** (**1_{red}** or **1_{ox}**), designated as eDAN, is based on our previously reported 2,7-diamido-1,8-naphthyridine (DAN) unit that forms a very stable⁸ and high-fidelity⁹ 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 **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 Cu₂O 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 **1_{red}** and **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 **1_{red}** with activated MnO₂.¹⁵ The reduction back to **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)ethylene-diaminocobalt(II) (salcomine)¹⁷ serve as catalysts for the O₂

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Table 1. Redox Chemistry of **1**^a

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 **1**_{red}. However, in the presence of **2**, only salcomine effected the conversion of **1**_{red} to **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 **1**_{red}·**2** complex and the low solubility of Cu(OAc)₂ in chloroform. The reduction of **1**_{ox} was effected by hydroquinone in 96% yield.

The abilities of **1**_{red} and **1**_{ox} to complex **2** were examined qualitatively by ¹H NMR spectroscopy (Figure 1). For the sake of clarity, CD₂Cl₂ 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 **1**_{red}. In contrast, the same protons shift minimally upon addition of **1**_{ox}. Quantitative complexation studies were performed with **1** and **2** in chloroform using isothermal titration calorimetry (ITC) (Figure 2). The **1**_{red}·**2** complex exhibited an apparent association constant (*K*_{assoc}) of 1.1 × 10⁶ M⁻¹. After correction for the weak dimerization of **2**, which causes the endothermic dip leading up to 1 equiv in the ITC curve, the actual value of *K*_{assoc} was found to be 1.4 × 10⁶ M⁻¹.^{11,14} Although the ITC data for **1**_{ox}·**2** did not allow the binding to be quantified, a ¹H NMR titration study afforded a corrected *K*_{assoc} of 6.7 × 10² M⁻¹ for **1**_{ox}·**2**. The large value of *K*_{assoc} for **1**_{red}·**2** is similar to that reported for the DAN·UG and DAN·DeUG complexes.

The more than 2 × 10³-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. 10⁴ M⁻¹.⁸ Two factors may readily account for the weaker binding by **1**_{ox}. First, simple modeling indicates that **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 **1**_{ox}·**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 supra-molecular 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

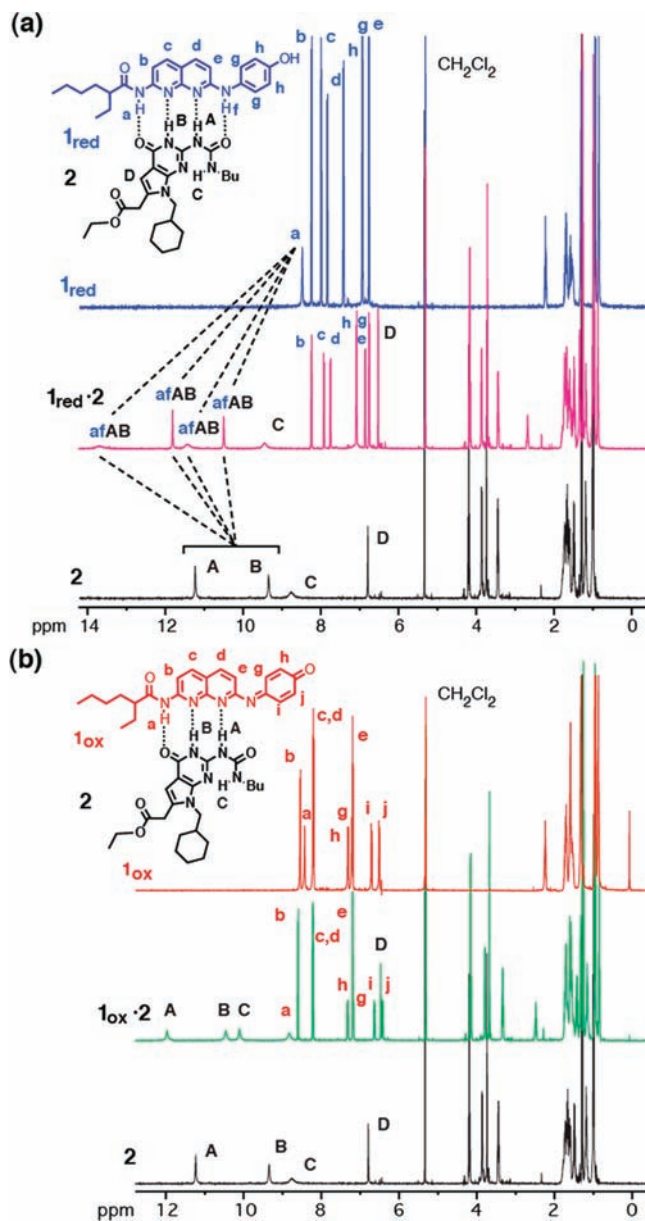


Figure 1. (a) ¹H NMR spectra (500 MHz, CD₂Cl₂, 295 K) of (top) **1**_{red}, (middle) **1**_{red}·**2**, and (bottom) **2** showing the changes to **1**_{red} and **2** upon association to form **1**_{red}·**2**. (b) ¹H NMR spectra (500 MHz, CD₂Cl₂, 295 K) of (top) **1**_{ox}, (middle) **1**_{ox}·**2**, and (bottom) **2**. The assignments in (a) and (b) are tentative. The **1**_{red}·**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 described¹² 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 ¹H 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

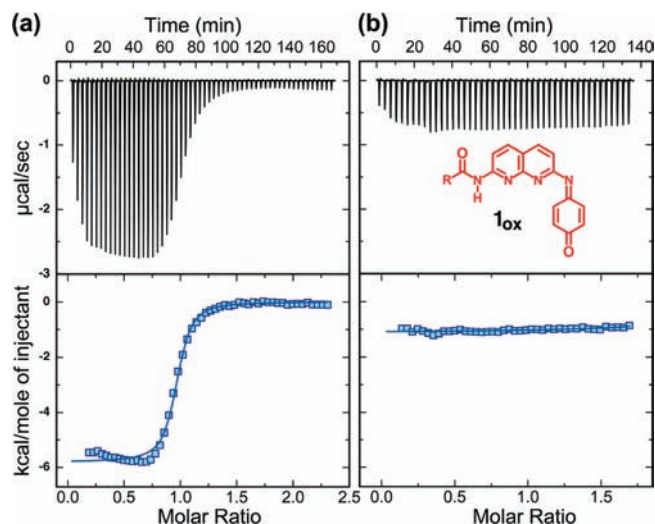
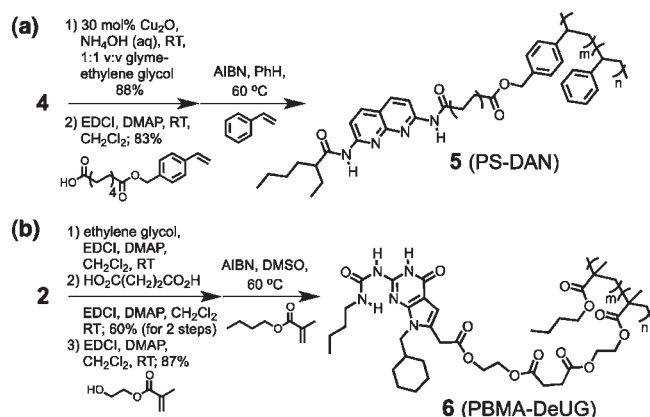


Figure 2. ITC data for (a) $1_{\text{red}} \cdot 2$ and (b) $1_{\text{ox}} \cdot 2$. A detailed discussion of the ITC data can be found in the SI.

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.

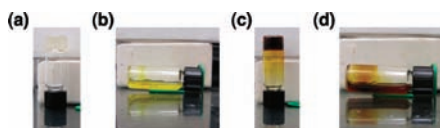


Figure 3. ¹⁴(a) Blend of PS-DAN and PBMA-DeUG. (b) Blend with 1_{red} added. (c) Reformation of viscous gel by oxidation of 1_{red} to 1_{ox} . (d) Redestruction of the polymer blend by reduction of 1_{ox} to 1_{red} .

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 1_{red} (ca. 100 equiv per DeUG unit), the gel was destroyed (Figure 3b). After treatment with salcomine (<0.5 equiv

with respect to 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 ^1H NMR spectroscopy, and control experiments were performed to confirm that the redox reagents were responsible for the 1_{red} to 1_{ox} interconversion and that this in turn controlled the formation of the supramolecular polymer blend.¹⁴ Multiple cycles were not examined, but in ^1H 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 $1_{\text{red}} \cdot 2$) but to bind weakly when oxidized ($-\Delta G^\circ = 3.8$ kcal mol⁻¹ for $1_{\text{ox}} \cdot 2$). 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

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

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