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LETTER

# A Reversible Supramolecular Assembly Containing Ionic Interactions and Disulfide Linkages

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**An ionic polymeric network based on a disulfide diphosphonium ionic liquid and a tetraanion was designed and studied in order to explore two self-assembly strategies: weak covalent bonds and ionic interactions. When the disulfide diphosphonium ionic liquid was complexed with a multianion, a crosslinked network structure was obtained. By applying external stimuli such as temperature or inducing a mild redox reaction, the network could be disrupted. The disruption / formation of the network is reversible. The thermal, rheological and electrochemical properties were also studied to further characterize these materials and to better understand the resulting structure-property relationships.**

Supramolecular polymers exhibit unique and interesting properties, and are of interest for the design of "smart" polymeric assemblies for use in fields ranging from biomaterials to energy transfer and storage.[1-4] The reversibility of the noncovalent bonds enables the monomer or polymer chains to assemble and disassemble.[5, 6] This characteristic affords controllable architectures with bulk properties that can respond to external stimuli.[7-10] For example under a shear force the polymer will disassemble into smaller units and then re-assemble once the force has been removed. Non-covalent interactions such as hydrogen bonding and metal-ligand coordination are extensively utilized, in contrast to ionic interactions, to construct such supramolecular polymers.[11,12] However, ionic interactions provide an attractive complementary approach for the facile preparation of supramolecular assemblies. Currently, this approach is being explored with combinations of small molecules, macromolecules, or mixtures of the two to afford polymer networks.[13-27]

Disulfide linkages are present in proteins, numerous natural products as well as in some drugs (e.g., leinamycin), and play important structural and functional roles.[28,29] For example, disulfide bond formation is critical for proper folding of proteins to afford activity and disulfide bond cleavage occurs in the endocytic pathway during intracellular protein degradation. The bond energy of the disulfide linkage is about 40% weaker than a typical covalent bond such as a carbon-carbon single bond. Like non-covalent bonds, the disulfide bond has a reversible and dynamic nature, and, therefore, can be utilized to construct functional supramolecular assemblies. A disulfide bond is formed by the oxidation reaction between two thiols and once formed it is susceptible to reduction or a disulfide-thiol exchange reaction.[30-32] Because of the reversible nature of the disulfide linkage, these linkages are used widely in the development of chemosensors, prodrugs, and nanomaterial drug carriers.[33-35]

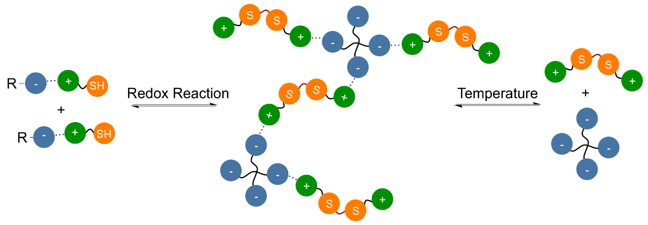

Figure 1. Schematic of the ionic network, **A**, formed between a disulfide diphosphonium and ethylenediaminetetraacetic acid (EDTA). The ionic network undergoes a reversible transition from a network to a non-network state in response to external stimuli, such as temperature, or a redox reaction. R represents the remaining network structure and disulfide reduction.

Herein, we designed an ionic polymeric network based on a disulfide diphosphonium and a tetraanion in order to investigate two self-assembly strategies: thiol/disulfide reactivity and ionic interactions (**A**, Figure 1). Supramolecular ionic networks are electrostatically crosslinked networks synthesized from multi-cations and multi-anions through ionic interactions while maintaining a charge ratio of 1:1. To synthesize a supramolecular network requires two different molecular structures whereby one structure possesses at least two and the other three or more molecular ionic recognition groups.[15] Specifically, we complexed the disulfide based diphosphonium ionic liquid with ethylenediaminetetraacetic acid (EDTA). This mixture afforded a network structure, **A**, with disulfide bonds present within the crosslinkers. Specifically, we report the synthesis of a thiol terminated phosphonium ionic liquid, its disulfide ionic liquid analog, and the thermal, rheological, and

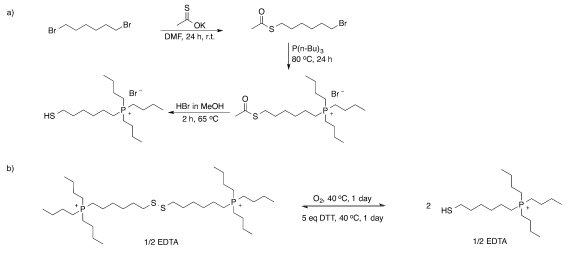

Figure 2. a) Synthesis of thiol-monophosphonium ionic liquid, **D**. b) Transformation between the disulfide-diphosphonium/EDTA network, **A**, and the thiol-monophosphonium/EDTA mixture, **B**.

electrochemical properties of the ionic liquids, the resulting mixture, and the self-assembled network along with demonstration of the reversibility of the network.

A mono-phosphonium ionic liquid (IL) with a single terminal thiol was prepared from 1,6-dibromohexane in three synthetic steps in 55% overall yield (Figure 2a). The resulting thiol-monophosphonium, **D**, was oxidized via exposure to oxygen to afford the disulfide di-phosphonium ionic liquid, **C**. Next, the dimer was mixed with EDTA and heated under vacuum to form the ionic network, **A**. As a control group, the thiol-monophosphonium, **D**, was also mixed with EDTA, and this composition, **B**, lacks a sufficient number of interactions to form a network. Dithiolthreitol (DTT) or oxygen was utilized to transition between the disulfide-diphosphonium/EDTA network (**A**) and thiol-monophosphonium/EDTA mixture (**B**) in situ via reduction and oxidation reactions (Figure 2b). A direct switch between the network and non-network states was investigated using this mild redox reaction strategy.

First, the thermal properties of the ILs and the resulting ionic network and ionic mixture with EDTA were investigated. DSC and TGA were performed to determine the glass transition temperature and decomposition temperature. According to the TGA results, the ILs **C** and **D** are thermally stable and did not decompose until 300 °C. When the ILs **C** and **D** were complexed with EDTA, the resulting compositions started to degrade at around 200 °C due to the decomposition of EDTA. DSC was performed by consecutive cooling and heating between -70 to 200 °C. As shown in Figure 3, the disulfide-diphosphonium IL, **C**, exhibited a lower glass transition temperature at -40 ℃ compared to the thiol-monophosphonium IL, **D**. Upon EDTA crosslinking with the disulfide-diphosphonium IL to form the network (**A**), the $T_g$ reduced to -50 °C. Likewise adding EDTA to the thiol-monophosphonium IL lowered the $T_g$ to -35 ℃. No melting peaks were observed in the DSC traces of A, B, C, or D (see SI for figure).

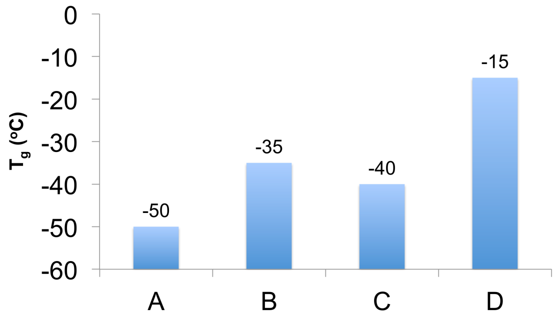

Figure 3. Glass transition temperatures of the ionic liquids (ILs) and ILs with EDTA: **A**: disulfide-diphosphonium/EDTA assembly (i.e., the network); **B**: thiol-monophosphonium/EDTA mixture; **C**: disulfide diphosphonium IL; and **D**: thiol monophosphonium IL.

One of the most important features of supramolecular networks that differentiate them from conventional covalently crosslinked networks, is that they are held together by reversible non-covalent interactions. Thus, rheometry was performed to investigate the viscosity change between the network and the non-network states as a consequence of a reduction reaction or weakening of the electrostatic interactions between the ion pairs via addition of thermal energy. All samples were dried at 80 °C overnight to remove any trace amount of water before evaluation. As shown in Figure 4, the viscosity of the mono-phosphonium ionic liquid, **D**, was low at around 7 Pa.s and only increased to 49 Pa.s when mixed with EDTA to form mixture **B**. In contrast, the viscosity of the disulfide-diphosphonium IL, **C**, was significantly higher at 2130 Pa.s. After addition of EDTA to the disulfide-diphosphonium IL, the viscosity value increased dramatically to about 4000 Pa.s, evidence of network formation, **A**. A diphosphonium IL such as $(Hexyl)_3PDecP(Hexyl)_3$, which lacks the disulfide linkage, when complexed with EDTA also gives a highly viscous material.[15] Likewise, after oxidation of the thiol-monophosphonium/EDTA mixture **(B)**, the viscosity significantly increased to 4110 Pa.s showing recovery of the disulphide-diphosphonium/EDTA network. These steps of oxidation and reduction can be repeated to give the low viscous non-network (i.e., **B** composition) and viscous network (**A** composition) states.

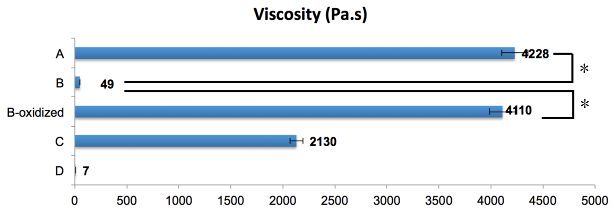

Figure 4. Viscosity measurements of the ionic liquids (ILs) and ILs with EDTA at 25°C (averaged, n = 3; strain = 1%; *f* = 1 Hz; *p < 0.001). **A**: disulfide-diphosphonium/EDTA assembly (i.e., the network); **B**: thiol-monophosphonium/EDTA mixture; **B-oxidized**: oxidized thiol-monophosphonium/EDTA assembly; **C**: disulfide diphosphonium IL; and **D**: thiol monophosphonium IL.

To study the reversibility of the disulfide-diphosphonium/EDTA network, **A**, resulting from ionic interactions, consecutive temperature sweep experiments were performed. The sample was dried at 80 °C overnight to remove water and was kept under $N_2$ during testing to avoid humidity. The temperature was increased from 10 °C to 90 °C, and then decreased back to 10 °C. The temperature cycle was repeated. In between each sweep, there was a 15-minute rest time to allow the network to reform. As expected, the viscosity

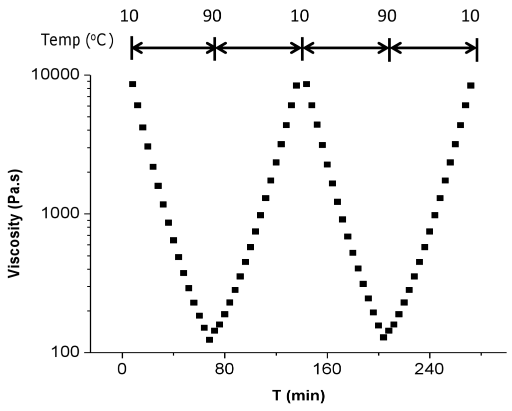

Figure 5. Results form the oscillatory temperature sweep experiment demonstrating the reversibility of the disulfide-diphosphonium/EDTA network, **A**.

decreased dramatically with increasing temperature and increased with decreasing temperature (Figure 5). This phenomenon was repeatable as the network recovered after being disrupted. The ionic network, **A**, exhibits good reversibility as measured by the viscosity data.

The conductivities of the ILs, mixtures, and networks were subsequently measured as a function of temperature to determine the relationship between temperature, viscosity, and conductivity. As shown in Figure 6, the conductivity of the thiol-monophosphonium IL, **D**, was greater than the disulfide-diphosphonium IL, **C**, and the conductivity values increased as the temperature increased. For example, at 120 °C, the conductivity of the thiol-monophosphonium IL, **D**, was more than 6 times higher than that of the disulfide-diphosphonium IL, **C**. Concurrently, the viscosity values for the thiol-monophosphonium IL, **D**, and disulfide-diphosphonium IL, **C**, decreased with temperature. As a general trend, as the temperature increased, the viscosity values reduced and conductivity values increased, demonstrating that viscosity is correlated to conductivity as charge transport occurs more readily in a less viscous material. For the thiol-monophosphonium IL (**D**), the viscosity decreased only from approximately 7 to 1 Pa.s as the temperature was increased from 25 °C to 80 °C. Even though this was a relatively small change in viscosity values, the conductivity values increased more than two orders of magnitude from 21.4 uS/cm to about 645 uS/cm. As the temperature was raised to 120 °C, the conductivity value further increased to 3300 uS/cm. Whereas for the disulfide-diphosphonium IL, **C**, the viscosity values decreased from 2130 Pa.s to 5.13 Pa.s upon going from 25 °C to 80 °C, and the conductivity increased from 0.62 uS/cm to about 90 uS/cm. The disulfide-diphosphonium/EDTA network (**A**) was viscous (≈ 4,000 Pa.s) at 25 °C and exhibited a low conductivity (<< 1 uS/cm). Its conductivity value increased with increasing temperature. When the network was completely disassembled at 90 °C, the conductivity value was 100 uS/cm.

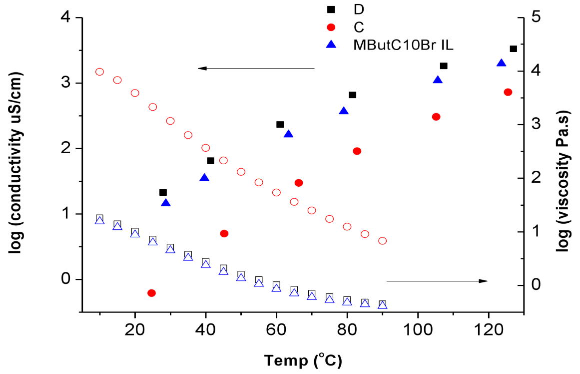

Figure 6. Conductivity-viscosity relationship of ionic liquids as a function of temperature.

In order to further investigate the high conductivity value measured for the thiol-monophosphonium IL (**D**), a non-thiol analog was synthesized and studied, where the terminal SH was replaced by a methyl group (MButC6Br). The viscosity of MButC6Br overlapped with that of the thiol from 25 °C to 80 °C due to its similar structure and size. However, the conductivity of the thiol was almost twice that of MButC6Br at 80 °C (1200 uS/cm *vs.* 800 uS/cm). The mechanism responsible for the high conductivity observed with **D** is under further investigation.

In conclusion, the design of a redox active ionic supramolecular assembly is described based on a new disulfide based diphosphonium ionic liquid and EDTA. Highly thermally stable viscous materials are observed due to the network formation. When the disulfide bonds are cleaved or the ionic interactions are disrupted, the assembled network is loss affording a freely flowing composition with lower viscosity and a higher conductivity. Combining the reversibility of the disulfide bond and the use of ionic interactions to create self-assembled networks, a direct switch between a network and a non-network state is realized using two different strategies.

## Experimental Section

All chemicals were purchased from Aldrich or Acros at highest purity grade and used without further purification. All reactions were performed under nitrogen atmosphere. $^{1}$H (400 or 500 MHz), $^{13}$C (101 or 126 MHz) and $^{31}$P (161 MHz) NMR spectra were recorded on Varian INOVA spectrometers. Electrospray mass spectra were obtained on an Agilent 1100 LC/MSD Trap with ESI and APCI sources. The thermalgravimetric analysis (TGA) measurements were performed with TGA Q50. The rheological measurement were performed on an AR 1000 Controlled Strain Rheometer from TA Instruments equipped with a Peltier temperature control using a 20 mm diameter parallel aluminum plate. The conductivity measurements were performed using a Conductivity Meter (K912, Consort) that has a 4-electrode cell to prevent the polarization error and fouling of the electrode. Please see the supporting information document for a complete description of the syntheses and the characterization studies.

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## Notes and references

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