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Proton transfer *versus* redox modulation in thiourea-phenanthrenequinone molecular and polymeric complexes†

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Phenanthrenequinone undergoes highly efficient proton transfer processes in the presence of a thiourea-funtionalised polystyrene copolymer whereas interactions with a similar benzyl-thiourea monomer show strong redox modulation of the quinone without proton transfer.

In nature, the interdependence between molecular recognition and redox processes provides a rational basis for the design and creation of biologically-inspired functional systems.[1] The relationship between proton transfer processes and specific non-covalent hydrogen bonding interactions is essential in governing multiple biological processes featuring both flavin-[2] and quinone-based[3] cofactors and has inspired numerous model systems.[4,5] Extension of this concept to man-made systems provides a test-bed for mechanistic hypotheses, as well as a starting point for the development of pragmatic devices.

Studies of quinone-urea-based models have been instrumental in understanding the complex redox processes that govern specific substrate–enzyme interactions.[6] For example, Smith and co-workers [6a] have shown that large positive shifts in the reduction potential of phenanthrenequinone (PQ) occurs upon exposure to a variety of ureas in aprotic solvents, where the magnitude of these shifts correlates well with the ability of the urea to act as a hydrogen bond donor. Research focused upon the engineering of macromolecular-scale systems, and from these simple urea-PQ models the development of dendrimers with redox tuneable hydrogen bonding properties has resulted ,[7] but this has yet to be extended to linear polymeric systems.

In this communication, we report the synthesis and characterisation of intramolecularly-associated polystyrene (PS) copolymers containing multiple thiourea binding sites. Electrochemical studies between these thiourea-substituted copolymers and phenanthrenequinone **1** give rise to highly efficient proton transfer processes, exhibiting model behaviours analogous to substrate–enzyme redox interactions. The 'polymer effect'[4a] in these linear systems is key to effecting the proton transfer process: quinone **1** readily undergoes highly efficient proton transfer processes in the presence of different thiourea-substituted polymers; however, interactions with a similar benzyl alkyl monomer shows strong redox-modulated hydrogen bonding[8] (Fig. 1).

Benzyl-thiourea **2** and thiourea-functionalised polystyrene copolymers (**3a**–**3c**) were synthesised through reaction of benzylamine or amine-functionalised polystyrene[9] with hexyl isothiocyanate. Phenanthrenequinone receptor **1** was purchased from Aldrich, Inc. and used without any further purification.

Gel permeation chromatography (GPC) was performed on substituted thiourea polymers **3a**–**c** in $CHCl_3$ (Table 1) to gain insight into the structures of the polymers in solution. As expected, all of the polymers adopt compact, folded structures in $CHCl_3$ as indicated by their low apparent molecular weights.[10] The folded structures can be attributed to multiple intramolecular hydrogen bonding interactions between the thiourea units on the polymer. As the ratio of thiourea units on the polymer decreases, the polymer begins to unfold and, thus, polymer **3c** adopts the most open structure.

Cyclic voltammetry (CV) studies of **1** recorded in a 0.1 M solution of NBu_4ClO_4[11] in CH_2Cl_2, revealed a quasi-reversible reduction wave at $E_{1/2}$ = −584 mV (*vs.* decamethylferrocene) corresponding to the **PQ**/**PQ**$^{\cdot-}$ redox couple (Fig. 2a).[12] Upon the addition of aliquots of benzyl-thiourea **2** to the electrolyte solution, a positive shift in the reduction potential of **1** was observed (Fig. 2a). Following the addition of 10 equiv. of **2**, a reversible peak shifted by +74 mV was observed ($E_{1/2}$ = −510 mV).

CV titrations of **1** with increasing concentrations of thiourea-functionalised polymers (**3a**–**3c**), however, gave rise to very different electrochemical behaviours. Upon addition of polymers

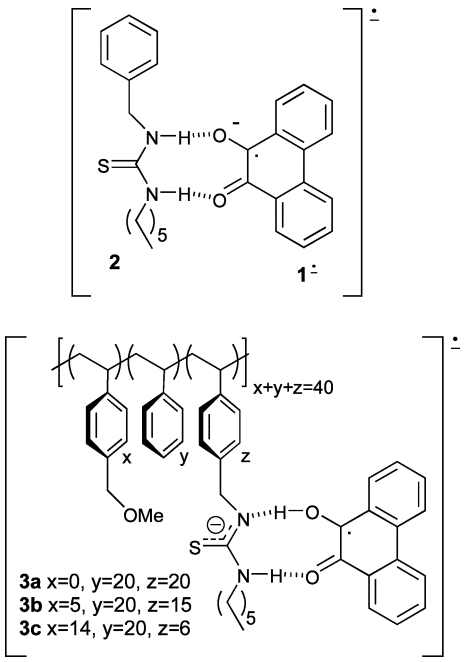

Fig. 1 Benzyl alkyl thiourea monomer **2** shows strong hydrogen bonding interactions with the radical anion of phenanthrenequinone **1**$^{\cdot-}$. In contrast, quinone receptor **1**$^{\cdot-}$ rapidly undergoes irreversible proton transfer in the presence of thiourea-functionalised, random polystyrene copolymers (**3a**–**3c**) at extremely low polymer equivalents.

Table 1 Gel permeation chromatography[a] (GPC) data for thiourea-functionalised polystyrene copolymers

Polymer	Thiourea units	M_n[a]
3a	20	640
3b	13	1490
3c	6	3100
Cl-Methyl-styrene (starting material)	0	5800

[a] GPC run in $CHCl_3$ (1mg ml^{-1}), PS standards.

† Electronic supplementary information (ESI) available: synthesis and ^{1}H NMR of thiourea polymers **3a**–**3c** and cyclic voltammograms of **1** in the presence of **2** (toluene/CH_2Cl_2). See http://www.rsc.org/suppdata/cc/b3/b312349a/

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3a–**3c** to a solution of **1**, irreversible proton transfer processes were observed in the CVs, as indicated by the disappearance of the re-oxidation wave of **1** (−495 mV cathodic peak) and the appearance of a new oxidation wave (+660 mV cathodic peak) from the newly formed hydroquinone (Fig. 2b). Although this observation was consistent for all three thiourea-substituted polymers, polymer **3c** functionalised with the least amount of thiourea and gave rise to the most efficient proton transfer (2 equiv. of polymer per thiourea unit). The other polymers required higher equivalents of polymer to induce proton transfer. An explanation for the rapid proton transfer that occurs between **3c** and **1** is evident from the structure of **3c** in solution as determined by GPC. Diffusion of the electroactive **1** is easier within polymer **3c** due to its more open structure. Incorporation of **1** within the folded structures of polymers **3a** and **3b** requires higher equivalents due to its compact nature and presumably slower diffusion rates of **1** into its interior.

Understanding the proton transfer processes that occur between **3a**–**3c** and **1** not only requires a detailed understanding of the polymers' 3D structures but also of the localised binding pocket, and whether or not the proton transfer observed within the interior of the polymers is the result of a structural or dielectric effect. To probe the possible dielectric contributions to proton transfer within the thiourea polymers, CV experiments were carried out using **2** and **1** in toluene (see ESI†). Toluene in this case serves to change the localised dielectric environment surrounding the **1.2** complex. Despite the presence of an excess of toluene (80/20 toluene/CH_2Cl_2 solution), the CV of **1** still exhibits reversible redox processes without any evidence of proton transfer. This result effectively demonstrates that the proton transfer between the thiourea-substituted polymers and **1** is not the result of localised environmental effects, and indicates that it is the cooperative organisation of the thiourea units within the binding pocket of the polymer that dictates the proton transfer. This behaviour is analogous to enzyme–substrate interactions in which complex redox processes only occur within a specific binding pocket.

In summary, we have shown that **1** readily undergoes highly efficient proton transfer processes in the presence of thiourea-functionalised polymers. However, when CV data for **1** were recorded in the presence of monomer **2**, proton transfer is not observed, and strong redox modulated hydrogen bonding occurs. Changing the localised dielectric environment surrounding thiourea monomer **2** and **1** fails to induce proton transfer processes, thereby supporting our hypothesis that the rapid proton transfer oberved between **1** and thiourea polymers **3a**–**3c** is a consequence of a cooperative organisation of the ureas within the polymer binding pocket. Thus, our thiourea-functionalised polystyrene copolymer complexes with **1** provide a model sytem for studying both redox enzymes and the 'polymer effect'.

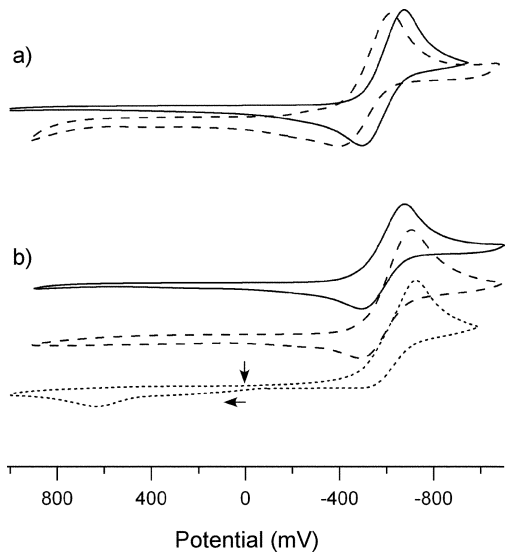

Fig. 2 (a) Cyclic voltammogram of **1** alone (—) and bound to thiourea monomer **2** (**---**) (10 equiv.). (b) Cyclic voltammograms of **1** recorded in the presence of different thiourea copolymers **3a** (—), **3b** (**---**), and **3c** (···) (2 equiv. based on thiourea functionality on the polymer chain). Scan rate = 100 mV s^{-1}.

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Notes and references

1 J. Nowick, M. Pairish, I. Lee, D. Holmes and J. Ziller, *J. Am. Chem. Soc.*, 1997, **119**, 5413; C. Nelsoney and Y. Kelly, *J. Am. Chem. Soc.*, 1996, **118**, 5836; Y. Kato, L. Toledo and J. Rebek, *J. Am. Chem. Soc.*, 1996, **118**, 8575; R. Cheng, S. Fisher and B. Imperiali, *J. Am. Chem. Soc.*, 1996, **118**, 11 349; A. Maynard, J. Sharman and S. Searle, *J. Am. Chem. Soc.*, 1998, **120**, 1996; E. Fan, C. Vicent and A. Hamilton, *New J. Chem.*, 1997, **21**, 81.

2 S. Ghisla and V. Massey, *Eur. J. Biochem.*, 1989, **181**, 1.

3 C. Anthony, *Biochem. J.*, 1996, **320**, 697.

4 (*a*) L. Liu and R. Breslow, *J. Am. Chem. Soc.*, 2002, **124**, 4978; (*b*) E. M. Seward, R. B. Hopkins, W. Sauerer, S. W. Tam and F. Diederich, *J. Am. Chem. Soc.*, 1987, **102**, 1783; (*c*) J. Hasford, W. Kemnitzer and C. Rizzo, *J. Org. Chem.*, 1997, **62**, 5244; (*d*) T. Akiyama, F. Simeno, M. Murakami and F. Yoneda, *J. Am. Chem. Soc.*, 1992, **114**, 6613; (*e*) Y. Yano, T. Kajiki and H. Ohshiro, in *Flavins and Flavoproteins '96*, K. Stevenson, V. Massey and C. Williams, ed., University of Calgary, Calgary, 1997, pp. 171–174.

5 A. Niemz and V. Rotello, *Acc. Chem. Res.*, 1999, **32**, 44; E. Breinlinger, A. Niemz and V. Rotello, *J. Am. Chem. Soc.*, 1995, **117**, 202; E. Breinlinger and V. Rotello, *J. Am. Chem. Soc.*, 1997, **119**, 1165; A. Niemz and V. Rotello, *J. Am. Chem. Soc.*, 1997, **119**, 6833.

6 (*a*) Y. Ge, L. Miller, T. Ouimet and D. K. Smith, *J. Org. Chem.*, 2000, **65**, 8831; (*b*) M. Greaves, A. Niemz and V. Rotello, *J. Am. Chem. Soc.*, 1999, **121**, 266; (*c*) C. Wilcox, E. Kim, D. Romano, L. Kuo, A. Burt and D. Curran, *Tetrahedron*, 1995, **51**, 621; (*d*) K. Haushalter, J. Lau and J. Roberts, *J. Am. Chem. Soc.*, 1996, **118**, 8891; (*e*) P. Smith, M. Reddington and C. Wilcox, *Tetrahedron Lett.*, 1992, 6085; (*f*) J. Albert and A. Hamilton, *Tetrahedron Lett.*, 1993, 7363; (*g*) M. Hughes and B. Smith, *J. Org. Chem.*, 1997, **62**, 4492.

7 G. Cooke, V. Sindelar and V. M. Rotello, *Chem. Commun.*, 2003, 752.

8 Two-point, hydrogen bonding associations between benzyl-thiourea **2** and phenathrenequinone **1** are expected to be weak under neutral conditions. ^{1}H NMR spectroscopy revealed that upon the addition of an excess of guest **1**, the two thiourea protons of **2** (alone located at 5.93 and 5.73 ppm in $CDCl_3$) had broadened significantly and shifted downfield by *ca.* 0.3–0.5 ppm.

9 F. Ilhan, M. Gray, K. Blanchette and V. M. Rotello, *Macromolecules*, 1999, **32**, 6159.

10 For examples of intramolecularly-associated folding in polymeric systems, see: L. Brunsveld, B. Folmer, E. Meijer and R. Sijbesma, *Chem. Rev.*, 2001, **101**, 4071; R. Deans, F. Ilhan and V. Rotello, *Macromolecules*, 1999, **32**, 4956.

11 Since perchlorates are powerful oxidising agents, they are potentially hazardous, especially when in contact with reducing materials. Extreme caution was exercised in the preparation of electrolyte solutions for CV studies: N. Sax and R. Lewis, *Dangerous Properties of Industrial Materials*, 7th edn., Van Nostrand Reinhold, New York, 1989, vol. 3.

12 Typical procedure: CVs were recorded for a CH_2Cl_2 blank, then for a solution of **1** and decamethylferrocene (as reference) in a TBAP solution (0.1 M), and finally for the same sample containing equivalents of thiourea monomer or thiourea polymer. All solutions were purged with Ar for several minutes prior to data collection. Differences in half-wave potentials were determined using square-wave voltammetry. All scans were recorded at a sweep rate of 100 mV s^{-1}, without iR compensation.