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Probing the solvent-induced tautomerism of a redox-active ureidopyrimidinone†

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A ferrocene-functionalised ureidopyrimidinone has been synthesised that can signal the solvent-induced tautomerism of the dimeric 4[1H]-pyrimidinone form to the monomeric 6[1H]-pyrimidinone form.

The construction of quadruple hydrogen bonded arrays from linear combinations of donor (D) and acceptor (A) units has attracted much attention in attempts to create supramolecular formulations with interesting materials chemistry applications.¹ For example, Meijer and co-workers have developed ureidopyrimidinone systems that have the propensity to form stable hydrogen bonded dimers *via* quadruple hydrogen bonded interactions.² Although these systems offer convenient synthesis and have successfully been incorporated as recognition elements in supramolecular complexes,³ macromolecules⁴ and self-assembled monolayers,⁵ their ability to exist in up to three different tautomeric forms complicates both their characterisation and application as

supramolecular building blocks (Fig. 1). These tautomeric forms result in the formation of either discrete monomeric species (6[1H]-pyrimidinone)⁶ or dimeric species *via* pre-organised DDAA (4[1H]-pyrimidinone) or DADA (pyrimidin-4-ol) arrays, respectively. Pre-organisation and the minimisation of repulsive secondary interactions within the DDAA motif of the 4[1H]-pyrimidinone form result in K_{dim} values in excess of 10^7 M^{-1} , whereas the pyrimidin-4-ol form typically has significantly lower K_{dim} values due to the onset of secondary repulsive interactions resulting from DADA arrays.

The relative ratios of the three tautomeric forms are dependent upon the solvent, concentration and the nature of the R and R' groups.² For example, it has been shown that the relative ratios of dimers formed from the 4[1H]-pyrimidinone *versus* the pyrimidin-4-ol form were influenced by the electronic properties of the functionality in the 6-position of these heterocycles. However, the ability to control and conveniently detect the conversion of the dimeric structures to the non-intermolecularly hydrogen bonded 6[1H]-pyrimidinone tautomer (or *vice versa*) is arguably the most important goal for developing systems with binary recognition properties. Here, we report the synthesis of compound **1**, that has a ferrocene moiety in the 6-position of the heterocycle, which facilitates the convenient monitoring of the solvent-induced tautomerism from the 4[1H]-pyrimidinone tautomer to the discrete monomers resulting from the 6[1H]-pyrimidinone tautomer, using either ¹H NMR spectroscopy or electrochemistry (Fig. 2).⁷

Compound **1** was synthesised as detailed in the ESI. X-Ray quality needle-like crystals were obtained by the slow evaporation of solvent from a concentrated solution of **1** in CH₂Cl₂ and acetone. Fig. 3 shows that this compound forms dimers in the solid-state through a DADA array resulting from the pyrimidin-4-ol form of the heterocycle.‡ This is in accordance with recent

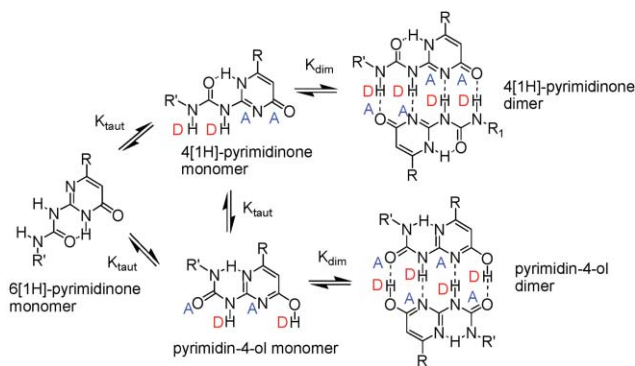


Fig. 1 Equilibria of the tautomeric forms of ureidopyrimidinones.

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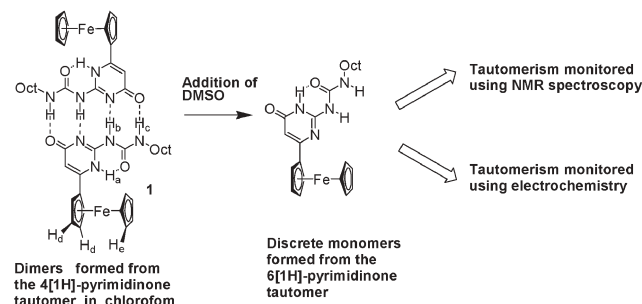


Fig. 2 Solvent-induced conversion of the 4[1H]-pyrimidinone tautomer to the 6[1H]-pyrimidinone tautomer for compound **1**.

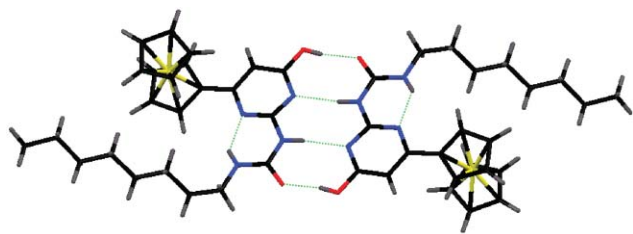


Fig. 3 X-Ray crystal structure of **1**, showing hydrogen bonded dimer formation *via* a DADA array resulting from the pyrimidin-4-ol form of the heterocycle.

reports of ureidopyrimidinones bearing electron donating groups in their 6-position.⁸ The outer hydrogen bonds O–H \cdots O ($d(\text{H}\cdots\text{A}) = 1.77(3)$ Å, $d(\text{D}\cdots\text{A}) = 2.583(2)$ Å, θ DHA = $168(3)^\circ$) are shorter than the inner hydrogen bonds O–H \cdots O ($d(\text{H}\cdots\text{A}) = 2.14(3)$ Å, $d(\text{D}\cdots\text{A}) = 3.013(3)$ Å, θ DHA = $171(2)^\circ$). The urea carbonyl group and the heterocyclic ring are near planar with the intramolecular hydrogen bond N–H \cdots N. The ferrocene unit appears not to undergo significant intramolecular interactions, however, a network of short contacts is observed between this unit and adjacent ferrocene, heterocycle, OH and alkyl groups. FT-IR spectra of **1** as a solid film or a KBr disk both reveal the presence of stretches consistent with the pyrimidin-4-ol (*e.g.* OH stretch at 3420 cm^{-1} and broad stretches at 2512 and 2572 cm^{-1} for O–H \cdots O=C) and 4[1H]-pyrimidinone tautomers (see ESI \dagger).² High-resolution solid-state ^1H - ^1H double-quantum MAS NMR experiments at 850 MHz also provided clear evidence for both the 4[1H]-pyrimidinone and pyrimidin-4-ol form in the solid-state, the approximate ratio of the two tautomers being 50 : 50. However, upon prolonged annealing (*e.g.* 391.5 K), the 4[1H]-pyrimidinone tautomer rearranges into the pyrimidin-4-ol form (see ESI \dagger).⁹

We next turned our attention to the elucidation of the structure of **1** in the solution state using NMR and FT-IR spectroscopy. ^1H NMR spectroscopy recorded in CDCl_3 clearly revealed the presence of a single tautomer, with downfield proton resonances of 13.6, 12.0 and 10.2 ppm being characteristic of strong hydrogen bonding interactions (Fig. 4a and ESI). Dilution studies performed on **1** revealed that the proton resonances between 10 and 14 ppm do not change, putting a lower limit on the dimerisation constant of **1** as $\sim 10^5\text{ M}^{-1}$. The positions of the resonances are in

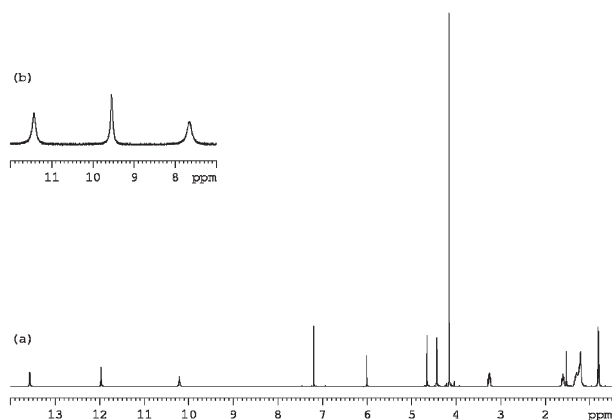


Fig. 4 ^1H NMR spectra of compound **1** in: (a) CDCl_3 and (b) $\text{DMSO}-d_6$.

accordance with previously reported data for the 4[1H]-pyrimidinone form.² Further evidence to support the 4[1H]-pyrimidinone structure in chloroform was obtained by recording the FT-IR spectra in this solvent (see ESI \dagger). In particular, the absence of OH and O–H \cdots O=C bands is particularly noteworthy.²

To gain further proof of the 4[1H]-pyrimidinone tautomer in the chloroform solution, we have recorded the NOESY and ROESY (see ESI \dagger) spectra in CDCl_3 . These experiments showed the presence of a cross-peak between the two urea protons (H_b and H_c). Furthermore, a cross-peak is observed between the intramolecularly hydrogen bonded proton (H_a) (13.6 ppm) and the ferrocene protons adjacent to the heterocyclic moiety (4.7 ppm). As these cross-peaks are consistent with the 4[1H]-pyrimidinone tautomer, we conclude that this tautomer exclusively exists in chloroform solution. When the ^1H NMR spectrum of compound **1** was recorded in pure $\text{DMSO}-d_6$, peaks consistent with a single tautomer were observed (Fig. 4b). As this tautomer only possesses one hydrogen bonded NH (11.5 ppm) and two non-hydrogen bonded protons at 9.5 ppm and 7.6 ppm, we conclude that, in accordance with previously reported data, the signals are due to the 6[1H]-pyrimidinone tautomer.²

With the 4[1H]-pyrimidinone tautomer confirmed in chloroform solution and the 6[1H]-pyrimidinone tautomer confirmed in DMSO, we next investigated whether the addition of aliquots of DMSO to a solution of **1** in chloroform could convert the 4[1H]-pyrimidinone to the 6[1H]-pyrimidinone form, and thus offer a facile method of disassembling the dimeric structure. The addition of aliquots of $\text{DMSO}-d_6$ to a solution of **1** in CDCl_3 resulted in two important changes in the ^1H NMR spectra. Firstly, the gradual disappearance of the original signals for H_a , H_b and H_c occurred with a concomitant reappearance of signals for these protons significantly upfield of their original position (see ESI \dagger). Secondly, the disappearance of the signals for protons H_d and H_e of the ferrocene moiety and the reappearance of new signals for these protons upfield of their original position were observed (Fig. 5). Upon addition of $\sim 30\%$ DMSO (v/v), a ^1H NMR spectrum consistent with that observed for **1** in pure $\text{DMSO}-d_6$ was observed. When experiments were repeated with acetyl ferrocene similar dramatic changes for protons H_d and H_e were not observed. Thus, the NMR spectral data for **1** show that the

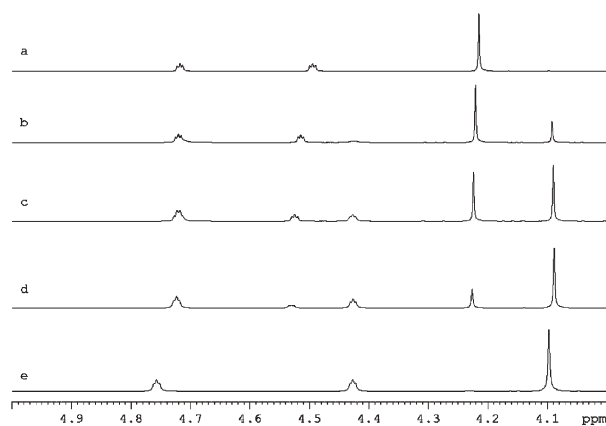


Fig. 5 (a) ^1H NMR spectrum of **1** in CDCl_3 ($\sim 1.6 \times 10^{-2}\text{ M}$) and upon the addition of aliquots of $\text{DMSO}-d_6$: (b) 8%, (c) 15%, (d) 23%, (e) 30%. Referenced to TMS = 0 ppm.

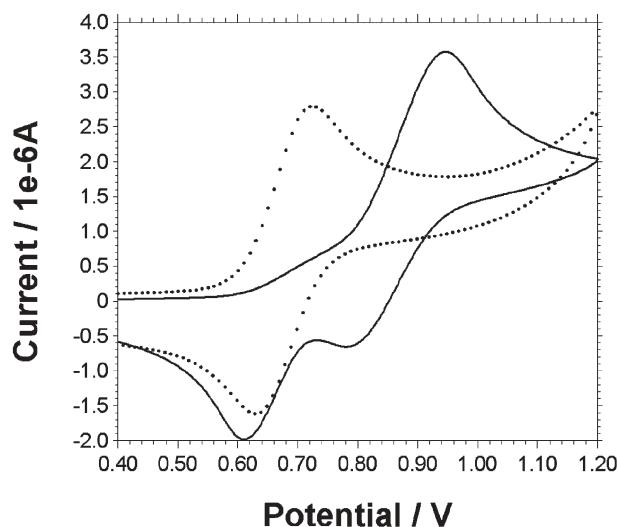


Fig. 6 CV data for compound **1** (5.5×10^{-4} M) recorded in CH_2Cl_2 (—) and upon the addition of 30% DMSO (···). Scan rate = 100 mV s^{-1} .

addition of 30% DMSO causes a solvent-induced conversion from the 4[1H]-pyrimidinone to the 6[1H]-pyrimidinone tautomer, which is signalled by profound changes in the microenvironment of ferrocene protons H_d and H_e that accompany this tautomerism.

As the NMR studies above indicated a substantial change in the ferrocene moiety upon the addition of DMSO, we next turned our attention to whether we could exploit the redox active nature of the ferrocene unit to monitor the 4[1H]-pyrimidinone to 6[1H]-pyrimidinone tautomerism electrochemically (Fig. 6). When the cyclic voltammetry (CV) of compound **1** was recorded in CH_2Cl_2 , a pseudoreversible redox wave was observed at $E_{1/2} = +0.86 \text{ V}$ and an irreversible redox wave $E = +0.65 \text{ V}$. We attribute the pseudoreversible wave to the hydrogen bonded 4[1H]-pyrimidinone dimer.¹⁰ When aliquots of DMSO were added to this solution, the pseudoreversible redox wave disappeared and a new reversible wave appeared at $E_{1/2} = +0.66 \text{ V}$ (30% DMSO, v/v), with the reduction wave overlapping the original irreversible wave observed in CH_2Cl_2 . As this redox wave is consistent with electrochemical data observed when the CV of compound **1** was recorded in DMSO only, we conclude that this wave corresponds to redox processes of the 6[1H]-pyrimidinone tautomer. In experiments that were undertaken with acetyl ferrocene only a $\sim 50 \text{ mV}$ negative shift of a reversible redox wave was observed under the same conditions, presumably a consequence of the increasingly polar environment that surrounds the ferrocene moiety. Therefore, we have shown that CV offers a convenient method for monitoring the profound changes in the electrochemical properties of the ferrocene unit that accompany the solvent-induced tautomerism.

In conclusion, we have shown compound **1** exists as the 4[1H]-pyrimidinone tautomer in chloroform solution and the 6[1H]-pyrimidinone tautomer in DMSO. Using NMR

spectroscopy, we have demonstrated that the addition of DMSO ($\sim 30\%$, v/v) to a solution of **1** in chloroform results in the formation of the discrete 6[1H]-pyrimidinone tautomer from the dimeric 4[1H]-pyrimidinone form. Moreover, CV studies have also shown that this process can be conveniently monitored electrochemically, which paves the way for the construction and convenient study of solvent-induced binary recognition properties of more complicated assemblies of **1** (e.g. surface confined and polymeric), where more traditional analytical techniques for monitoring tautomerism (e.g. NMR spectroscopy) are less appropriate.

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‡ CCDC 638903. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b703070c

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