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Use of an Electrochemically-Induced Proton-Coupled Electron Transfer Reaction to Control Dimerization in a Ureidopyrimidone 4 H-Bond Array

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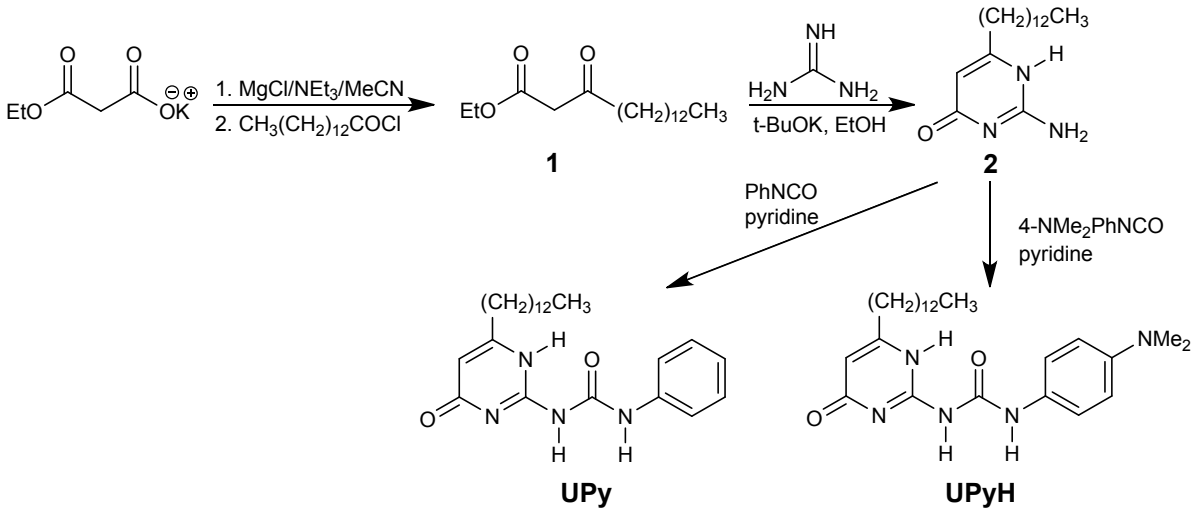
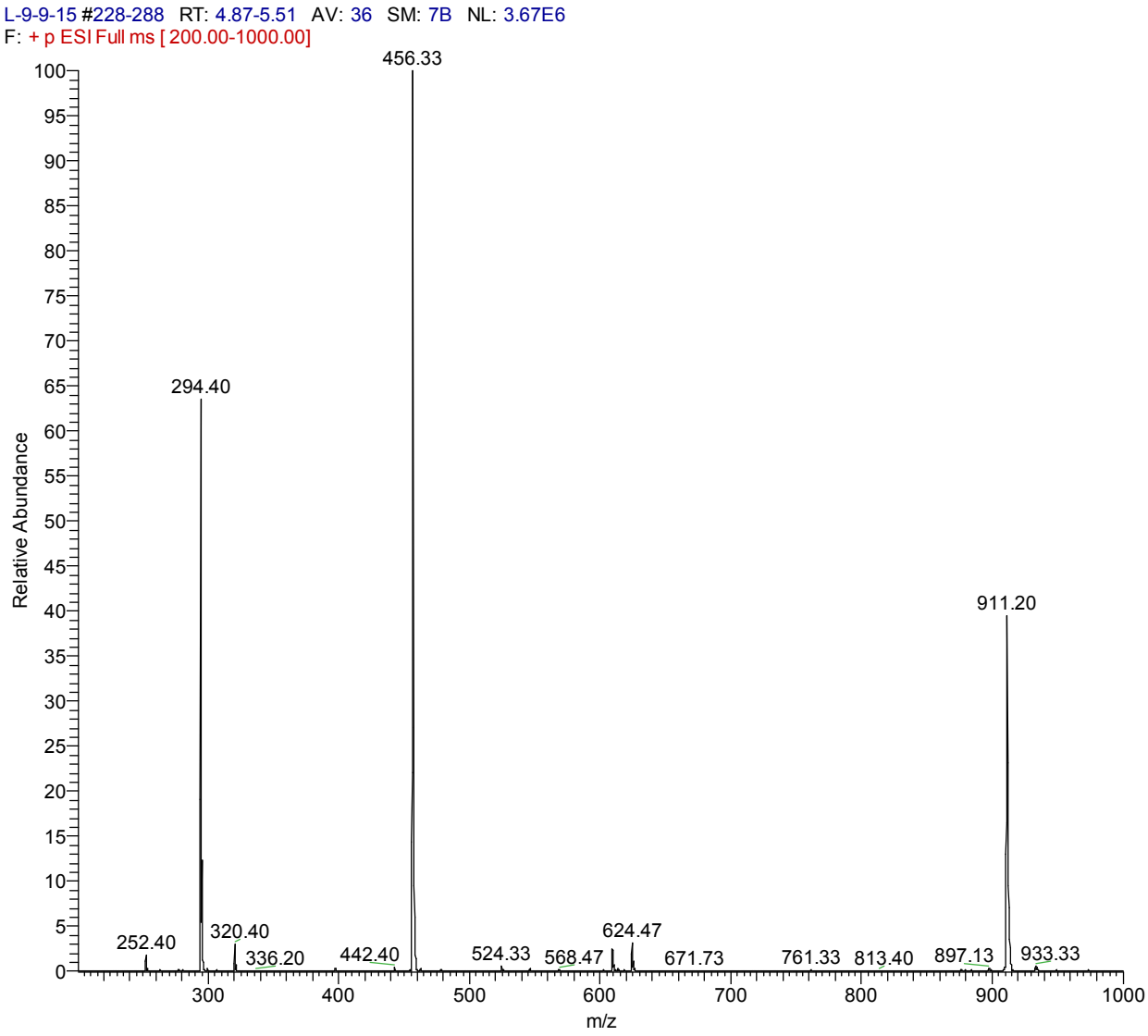
Scheme S1. Synthesis of UPyH and UPy



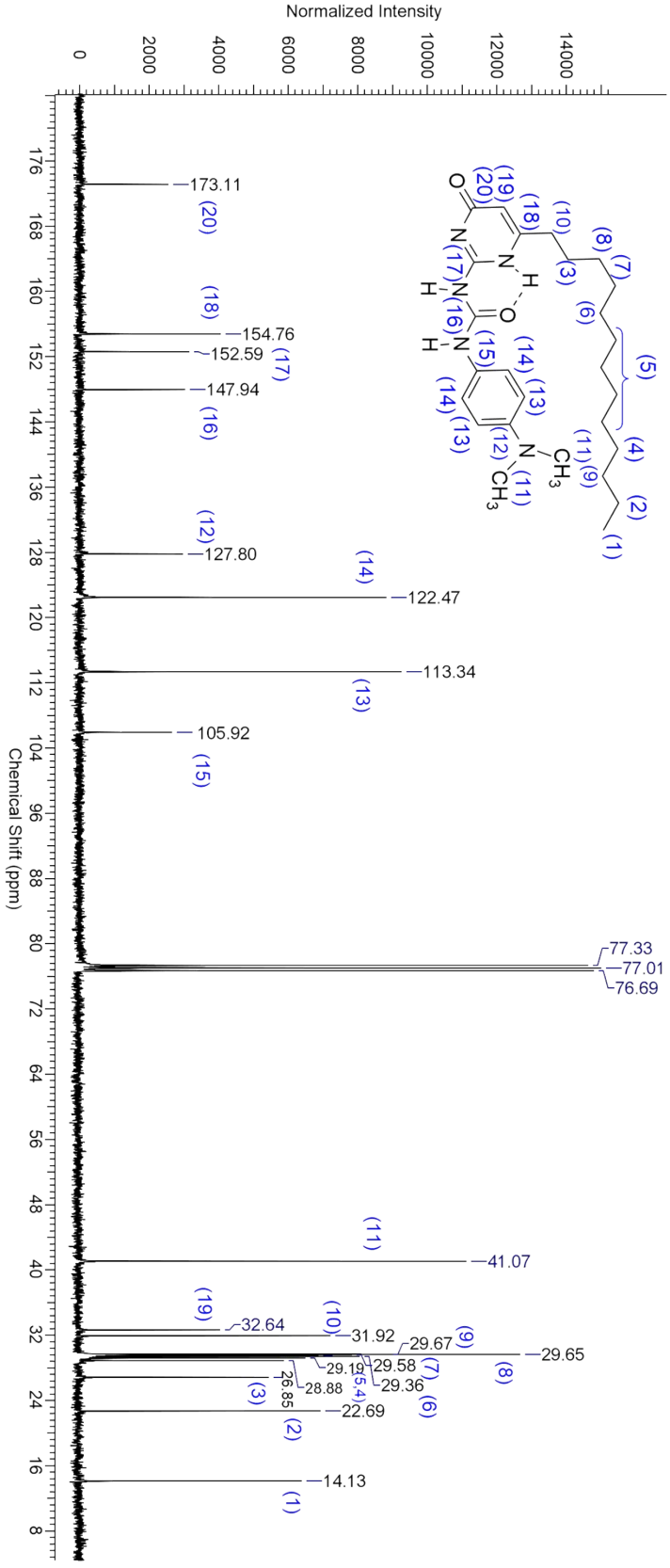
Synthetic Procedures. The synthesis of both UPyH and the electroinactive derivative, UPy, followed the general procedure used by Meijer shown in Scheme S1.[1] The first intermediate, the C_{13}-substituted β-Oxo ester **1**, was prepared following the procedure of Clay et al.,[2] in which addition of anhydrous $MgCl_2$ and triethylamine to potassium ethyl malonate was followed by the addition of myristoyl chloride. The C_{13}-substituted β-oxo ester was then placed into a solution of guanidinium carbonate, potassium tert-butoxide and anhydrous ethanol for a 48 hour reflux yielding 6-tridecylisocytosine, **2**, as presented by DeGreef et al.[3] Following recrystallization in 2-propanol, this intermediate was then reacted with either phenylisocyanate to give UPy or 4-dimethylaminophenylisocyanate to give UPyH. Spectra of UPy matched that previously reported by Meijer.[1] Meijer's group also synthesized the NEt_2 derivative of UPyH, but the NMe_2 derivative has not been previously reported.

Conversion of 2 to UPyH. 6-Tridecylisocytosine, **2**, vacuum dried at 90 °C (0.104 g, 0.354 mmol) was placed in a round bottom flask. The flask was then evacuated and back-filled 3x with Ar gas before anhydrous pyridine (2 mL) was added. To this solution 4-(dimethylamino)phenyl isocyanate (0.0857g, 0.528 mmol) purchased from Acros Organic was added. The reaction mixture was then refluxed for 4 hours. After cooling to room temperature Millipore purified water was added dropwise until all of a gummy off-white solid had precipitated. A solution of 20:10:1 of acetone:water:ethanol, v/v/v, was then added dropwise to the gummy precipitate until a fully solid precipitate formed. Recrystallization was conducted with a solution of acetone:ethanol, 1:1 v/v. If needed flash chromatography was conducted using 8:6:1, v/v/v CH_2Cl_2:hexane:MeOH in order to separate bis-1,4-p-(dimethylamino)phenyl urea (from decomposition of the isocyanate) from the product (0.09328 g, 57.8% yield). M.P. = 134-137 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 13.13(s, 1H), 12.197(s, 1H), 11.96(s, 1H), 7.51(d, 2H), 6.75(d, 2H), 5.85(s, 1H), 2.92(s, 6H), 2.38(tr, 2H), 1.60(m, 2H), 1.27(m,br 20H), 0.89(tr, 3H) ^{13}C NMR (400 MHz, $CDCl_3$) δ:179.13, 154.76, 152.61, 147.95, 127.81, 122.48, 113.35, 105.93, 41.07, 32.64, 31.93, 21.19-29.68 (multiple peaks), 28.89, 26.85, 22.70, 14.13. MS(ESI): 911(2M+1), 456(M+1).

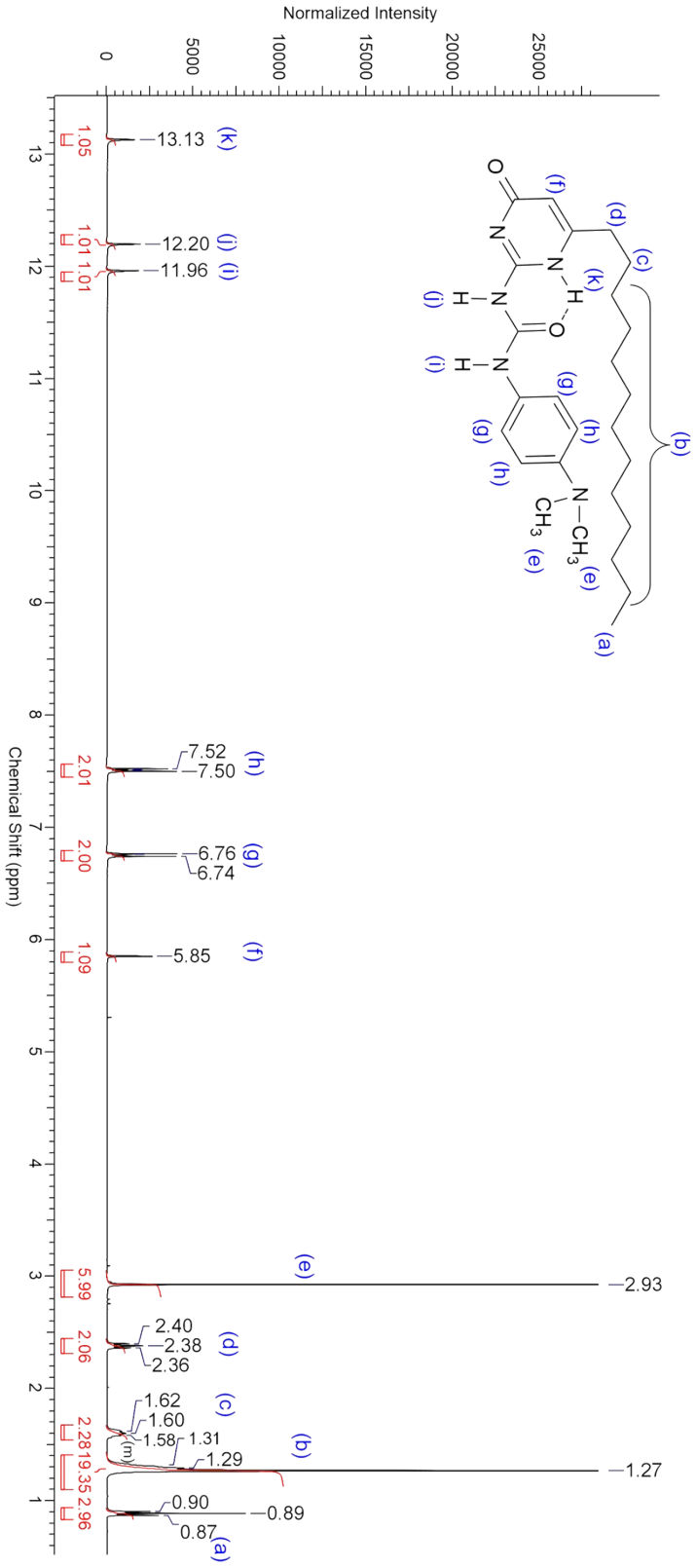
Mass Spectrum of UPyH



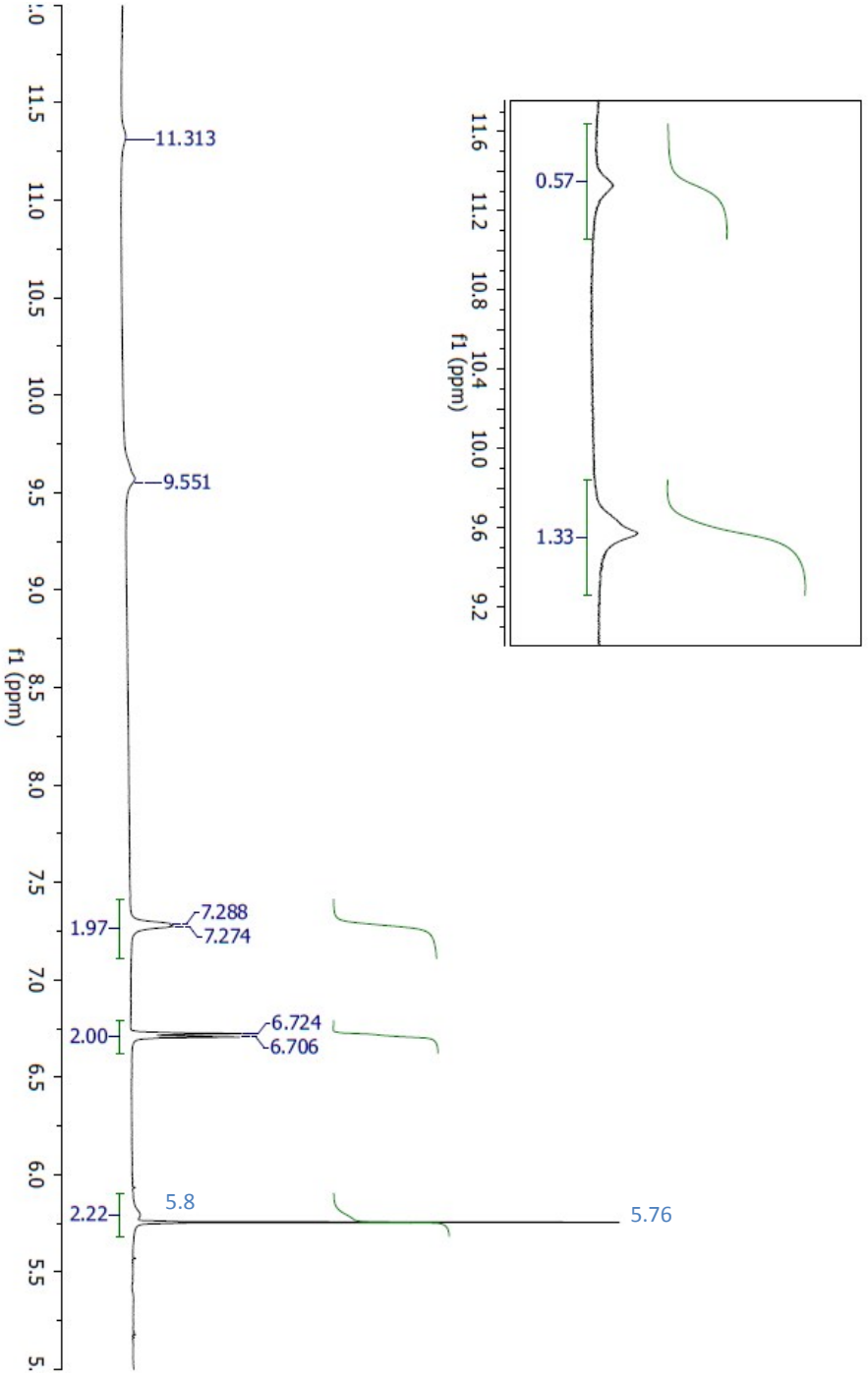
^{13}C NMR of UPyH ($CDCl_3$)



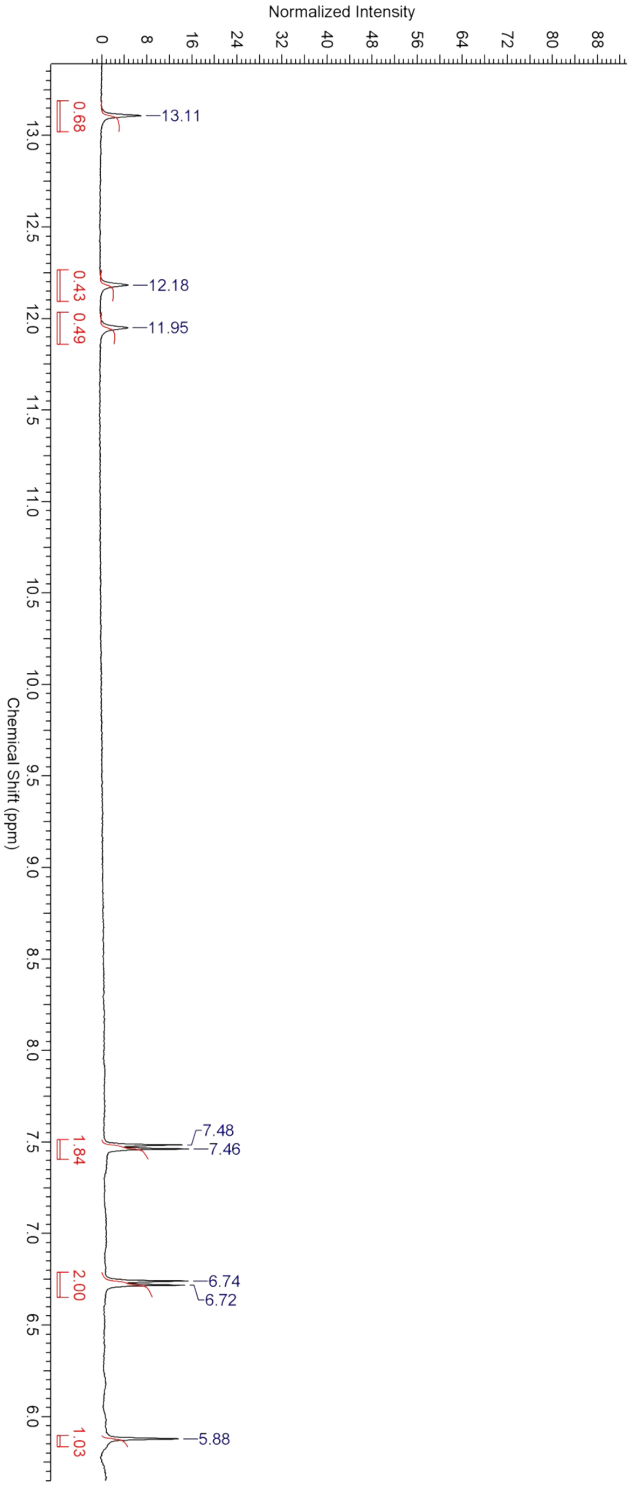
^{1}H NMR of UPyH ($CDCl_3$)



^{1}H NMR of 1 mM UPyH in 0.1 M NBu_4PF_6/d_6-DMSO



^{1}H NMR of 1 mM UPyH in 0.1 M NBu_4PF_6/CD_2Cl_2



Electrochemistry Procedures. The general voltammetry procedures along with those used for the concentration dependent studies and the UV-vis spectroelectrochemical work have been previously described.[4] All experiments, with the exception of the UV-vis study, were carried out in a N_2-atmosphere dry box using a Pt disk working electrode (area = 0.028 cm^2).

Sequential UV-Vis Spectra. The sequential UV-vis spectra shown in Figures 3 and 4 in the main paper were obtained using a Cary 50 UV-vis spectrophotometer and a previously described home-made Optically Transparent Thin Layer Electrochemical (OTTLE) Cell.[4] Briefly, the OTTLE cell uses a Au-plated W grid electrode to electrolyze a thin layer (~0.33 mm) of electrolyte solution in the beam path of the spectrophotometer. To obtain the sequential spectra, the Au grid working electrode was first scanned at a slow scan rate of 0.2 V/s through the voltage range in which the UPyH is oxidized and reduced in order to determine appropriate potentials to record spectra. The cell was then flushed with fresh solution, and a spectrum of the fully reduced UPyH recorded. Next, the electrode potential was again scanned positive at 0.2 V/s starting from a value positive of the onset of UPyH oxidation. The CV scan was paused at a potential in between the two oxidation waves and held at this value while spectra were recorded every 14.25 seconds from 800 nm to 230 nm at a scan rate of 2400 nm/min. After a total of 8 spectra, the potential was then stepped to value positive of the second oxidation and another series of spectra recorded using the same parameters.

CV Titration. To obtain a clearer understanding of the product resulting from the first electron transfer process, an electrochemical titration study with the electroactive UPyH added to a electroinactive UPy ($R_1 = (CH_2)_{12}CH_3$, R_2 = Ph) was conducted. The electrolyte solution used for this experiment was prepared beforehand in the dry box by placing 3.87 g of NBu_4PF_6, that was previously vacuumed dried at 100 °C overnight, into a 100 mL flask whereupon 100 mL of CH_2Cl_2 that had been previously dried by distillation with calcium hydride and running through a column of activated alumina was added. The electrolyte solution was then allowed to sit on activated 3A molecular sieves for at least 48 hours before use.

Stock solutions containing 4 mM of the electroinactive UPy and 3mM of electroactive UPyH were made just prior to the experiment by adding the required mass for each into their own 2 mL volumetric flasks and placing them into the dry box. The stock solution of electroinactive UPy was made first by diluting to the mark with the previously prepared CH_2Cl_2 electrolyte solution. This was then used to add sufficient electroinactive UPy to the flask containing electroactive UPyH to make a mixed 1 mM UPy, 3 mM UPyH stock solution after filling to the mark with electrolyte. This was done in order to minimize dilution effects on current height for the voltammetry of the electroactive UPyH.

Initial CV scans were conducted following an established routine for all electrochemical experiments. This included first achieving stable background CV scans using electrolyte solution only by alternating 20 cycles at 1 V/s with 1 cycle at 0.2 V/s, until CV overlays at 0.2 V/s showed no changes between scans. Once this was achieved, sufficient electroinactive UPy was added to the electrochemical cell from the UPy only stock solution to make a 1 mM electroinactive UPy electrolyte solution. Background scans were then run at 0.2, 0.5, 1, 2, 5 and then back to 0.2 V/s. Next, electroactive UPyH was titrated into the electrochemical cell using the 1 mM UPy, 3 mM UPyH stock solution to give following ratios of electroinactive UPy to electroactive UPyH: 100:1, 50:1, 25:1, 10:1, 5:1 and finally 1:1. After each addition, CV scans were run at 0.2, 0.5, 1, 2, 5 and then back to 0.2 V/s.

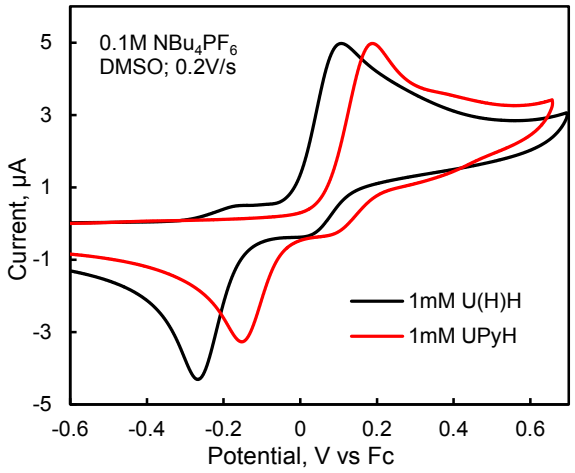


Figure S1. CVs (0.2 V/s) of 1 mM U(H)H and 1 mM UPyH in 0.1 M NBu_4PF_6/DMSO.

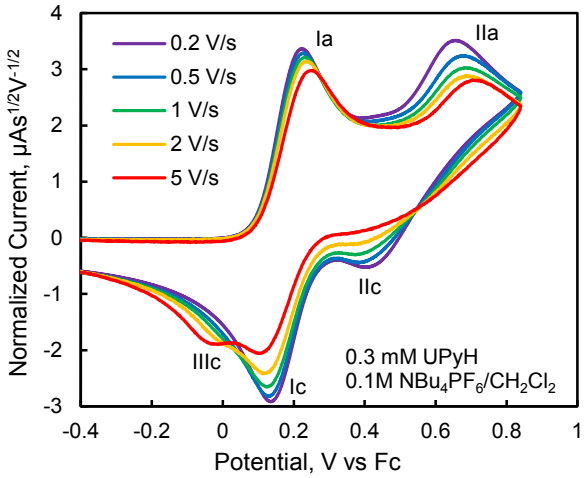


Figure S2. Background-subtracted CVs of 0.3 mM UPyH in 0.1 M NBu_4PF_6/CH_2Cl_2 at different scan rates. The currents have been normalized by dividing by the square root of the scan rate.

Scan rate Dependence of UPyH CVs in CH_2Cl_2. Figure S2 shows normalized CV's for 0.3 mM UPyH at different scan rates in in 0.1 M NBu_4PF_6/CH_2Cl_2. Note that as the scan rate increases, allowing less time for the reactions to take place, the chemical reversibility of Wave II is lost and a new reduction peak, IIIc, grows in at a potential negative of wave Ic. From our previous work with U(H)H,[4] this where we expect to see the reduction of the quinoidal cation. This supports the hypothesis that the UPyH quinoidal cation is one of the products formed after oxidation in peak IIa.

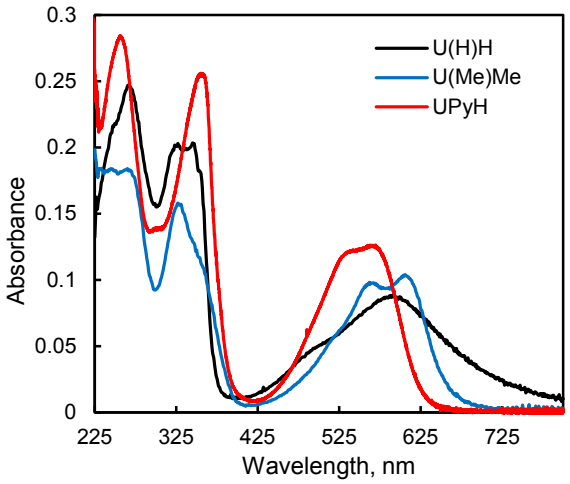
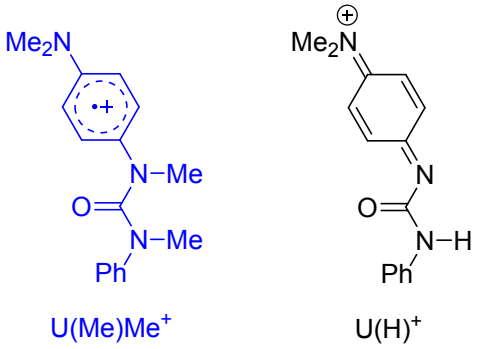
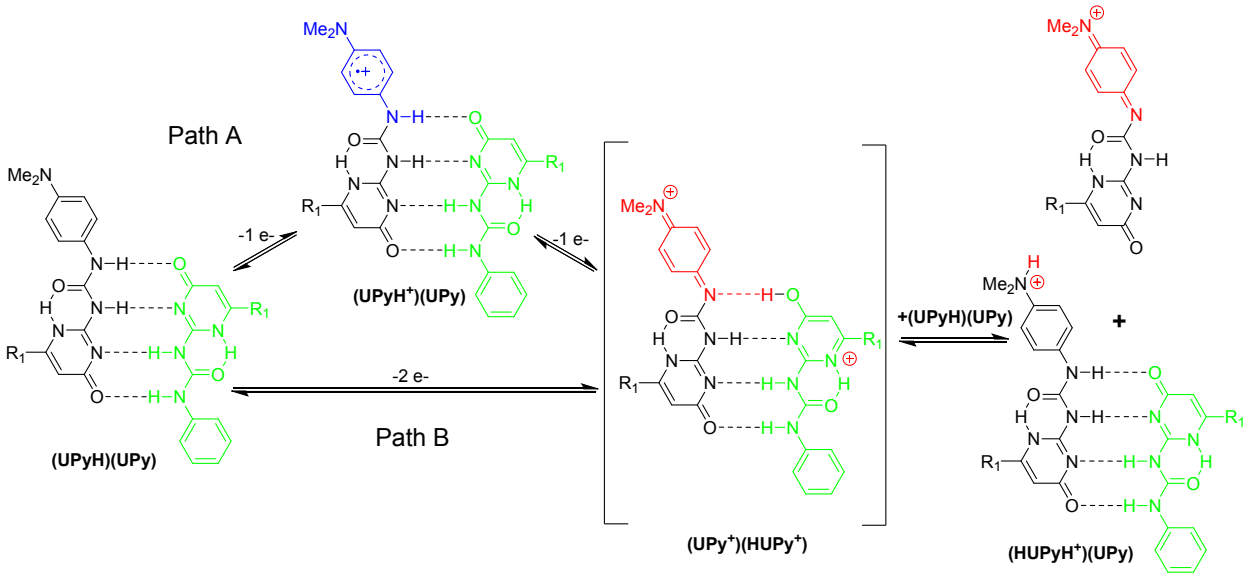


Figure S3. UV-vis spectra obtained in a thin layer spectroelectrochemical cell after the first oxidation of 0.5 mM U(H)H, U(Me)Me and UPyH in 0.1 M NBu_4PF_6/CH_2Cl_2.



Spectroelectrochemical data for the UPyH intermediate formed in the first oxidation. Figure S3 shows UV-vis spectra obtained in a thin layer spectroelectrochemical cell after the first oxidation of U(H)H, U(Me)Me and UPyH in 0.1 M NBu_4PF_6/CH_2Cl_2. The spectrum of U(H)H (in black) corresponds to the quinoidal cation, $U(H)^+$, and that of U(Me)Me (in blue) to the radical cation, $U(Me)Me^+$. Comparison of these spectra to that obtained after the first oxidation of UPyH (red spectrum) shows that the UPyH intermediate appears to be a radical cationic species and not a quinoidal cation.

Scheme S2. Possible Overall Oxidation Reactions for the Heterodimer Formed from Electroactive UPyH and Electroinactive UPy



Titration of Electroinactive UPy with Electroactive UPyH. In order to determine whether the initial oxidation of UPyH in CH_2Cl_2 corresponds to 1 e^- oxidation of both UPyH's in the dimer or 2 e^- oxidation of one of the UPyH's accompanied by proton transfer to the other, a CV titration experiment was run to see how the CV changes as an electroinactive UPy (no NMe_2 group on the phenyl, shown in green in Scheme S2) is titrated into a solution of the electroactive UPyH. As the concentration of the electroinactive UPy increases, more of the UPyH will be hydrogen bonded to it giving the heterodimer (UPyH)(UPy), Scheme S2. As illustrated in Scheme S2, in contrast to the homodimer, oxidation of the heterodimer will give distinctly different results depending on whether the reaction follows Path A or Path B. If the reaction follows Path A, going through the radical cation dimer, the CV of the heterodimer would still show a 1 e^- per UPyH oxidation followed at more positive potentials by a second oxidation of half height. This is because it will be thermodynamically favorable for the protonated electroinactive $HUPy^+$ formed after the second oxidation to transfer the acidic proton to the NMe_2 on a reduced UPyH resulting in its deactivation. This means the second oxidation involves 1 e^- per 2 UPyH. However, if the reaction follows Path B in Scheme S2 then the electroactive UPyH will be completely oxidized in the first step. Transfer of the acidic proton to a reduced UPyH would keep the wave height at 1 e^- (2e^- per 2 UPyH), but the second CV wave will be gone since all of the UPyH would be fully oxidized in the first wave.

Due to solubility issues, the actual titration experiment was done in reverse, with the electroactive UPyH titrated into a solution of the electroinactive UPy. The resulting CV's were background subtracted and normalized by dividing by the concentration of UPyH. The results, Figure S4, show no significant change in the height of either wave as the ratio of electroinactive to electroactive increases, consistent with what would be expected if Path A in Scheme S2 was followed, and ruling out Path B.

Another interesting observation in Figure S4 is the shift in the potential of the second oxidation to a less positive value at higher UPy to UPyH ratios where the heterodimer dominates. It makes sense that it would be easier to oxidize the radical cation in the heterodimer than the homodimer since in the former the binding partner is the uncharged reduced UPy, whereas in the latter the binding partner is another radical cation.

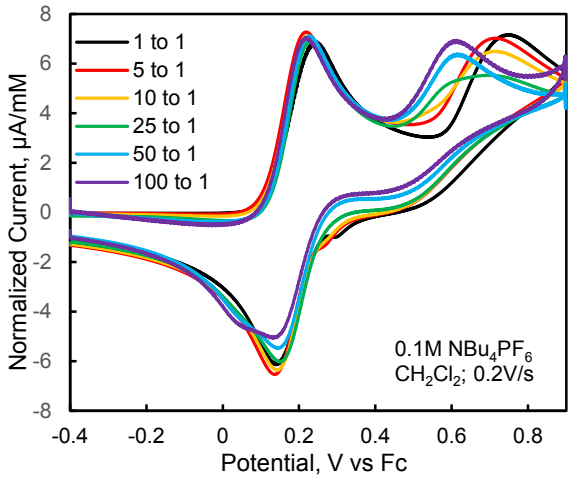


Figure S4. Background-subtracted CVs (0.2 V/s) of 0.01 mM (purple), 0.02 mM (blue), 0.04 mM (green), 0.10 mM (yellow), 0.20 mM (red) and 1 mM (black) UPyH in a 1 mM electroinactive UPy/0.1 M NBu_4PF_6/CH_2Cl_2 solution. The currents were normalized by dividing by the concentration of UPyH in each scan.

References

(1) Beijer, F. H.; Sijbesma, R. P.; Kooijman, H.; Spek, A. L.; Meijer, E. W. *J. Am. Chem. Soc.* **1998**, *120*, 6761-6769.

(2) Clay, R. J.; Collom, T. A.; Karrick, G. L.; Wemple, J. *Synthesis-Stuttgart* **1993**, 290-292.

(3) de Greef, T. F. A.; Nieuwenhuizen, M. M. L.; Stals, P. J. M.; Fitie, C. F. C.; Palmans, A. R. A.; Sijbesma, R. P.; Meijer, E. W. *Chem. Commun.* **2008**, 4306-4308.

(4) Clare, L. A.; Pham, A. T.; Magdaleno, F.; Acosta, J.; Woods, J. E.; Cooksy, A. L.; Smith, D. K. *J. Am. Chem. Soc.* **2013**, *135*, 18930-18941.