Supplementary Material (ESI) for Chemical Communications

Exploring the pH dependence of viologen reduction by α-carbon radicals derived from Hcy and Cys

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Supplementary Information

The preparation of viologens was performed under a nitrogen atmosphere in oven- and/or flame-dried glassware using a Vacuum Atmospheres drybox or by using standard Schlenk techniques. Solvents used as reaction media were distilled immediately before use: acetonitrile was distilled from Na/benzophenone ketyl. Ethyl bromoacetate was purchased from Alfa Aesar, NMR solvent (D_2O) was purchased from Cambridge Isotope Laboratories, Inc. All of the other reagents were purchased from Sigma-Aldrich and used without any further purification.

^{1}H spectra was recorded on a Bruker AV-400 (400 MHz ^{1}H) spectrometer in deuterated solvents using the solvent residual protons as an internal reference (H_2O: 4.68 ppm, $CDCl_3$: 7.26 ppm ^{1}H) for ^{1}H NMR or using DSS as an internal reference for ^{13}C NMR ($CDCl_3$: 77.0 ppm, t for ^{13}C NMR). Chemical shifts (δ) are given in parts per million down from tetramethylsilane (TMS). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quin =quintet, dd = doublet of doublets, dt = doublet of triplets, ddd = doublet of doublet of doublets, ddt = doublet of doublet of triplets, m = multiplet), coupling constant (Hz), and integration.

General Procedure[1] for the preparation of viologens: A mixture of alkyl bromide (10 equiv) and 4,4'-bipyridine (1 equiv) were heated to reflux in anhydrous acetonitrile under nitrogen for 4 to 20 hours. After the reaction mixture was cooled down to room temperature, the precipitate was filtered off and purified by recrystallization from ethanol.

1,1'-Bis(cyanomethyl)-4,4'-bipyridinium dibromide (entry 2):[2] Under Ar atmosphere 4,4'-bipyridine (0.781g, 0.05 mol) and 2-bromo acetonitrile (1.799g, 0.015 mol) were dissolved in anhydrous DMF (50 mL). The mixture was heated at 60 ^oC/16h,

then cooled to room temperature. 200 mL of acetone were added and the reaction mixture allowed to stand overnight at room temperature. The yellow precipitate was filtered, washed with acetone, and dried under vacuum. The product (1.46g, 74%) was obtained as a yellow powder. ^{1}H NMR (400 MHz, D_2O): δ 9.26 (d, J = 7.0 Hz, 4H), 8.64 (d, J = 7.0 Hz, 4H), 5.98 (s, 4H, diminished integration due to partial deuterium exchange). ^{13}C NMR (100 MHz, D_2O): δ 154.2, 148.8, 130.4, 115.3, 50.7.

1,1'-Bis(2-ethoxy-2-oxoethyl)-4,4'-bipyridinium dibromide (entry 3): Following the general procedure, ethyl bromoacetate (3.55 mL, 0.032 mol) and 4,4'-bipyridine (0.50 g, 0.0032 mol) were refluxed in anhydrous acetonitrile (60 mL) for 20 hours. The product (1.24 g, 80%) was obtained as cubic yellow crystals. ^{1}H NMR (400 MHz, D_2O): δ 9.07 (d, J = 6.4 Hz, 4H), 8.59 (d, J = 6.4 Hz, 4H), 5.63 (s, 4H, diminished integration due to partial deuterium exchange), 4.29 (q, J = 7.1 Hz, 4H), 1.24 (t, J = 7.1 Hz, 6H). ^{13}C NMR (100 MHz, D_2O): δ 169.3, 153.7, 149.6, 129.6, 66.8, 63.7, 15.8.

1,1'-Diallyl-4,4'-bipyridinium dibromide (entry 6): Following the general procedure, allyl bromide (1.77 mL, 0.02 mol) and 4,4'-bipyridine (0.32 g, 0.002 mol) were refluxed in anhydrous acetonitrile (40 mL) for 4 hours. The product (0.53 g, 65%) was obtained as deep yellow needles. ^{1}H NMR (400 MHz, D_2O): δ 9.03 (d, J = 6.8 Hz, 4H), 8.48 (d, J = 6.8 Hz, 4H), 6.19 (m, 2H), 5.51 (dd, J_1 = 10 Hz, J_2 = 17 Hz, 4H), 5.26 (d, J = 6.4 Hz, 4H). ^{13}C NMR (100 MHz, D_2O): δ 152.9, 148.1, 132.1, 129.6, 126.3, 66.2.

4,4'-dipyridyl 1,1'-dioxide: Following the literature procedure[3], 4,4'-bipyridine (5 g, 0.032 mol) in glacial acetic acid (25 mL) was heated to 70℃. After complete dissolution of the bipyridine, a 30% solution of H_2O_2 in H_2O (3.64 g, 0.032 mol) was added dropwise, and the mixture was stirred at 70 ℃ for 6 hours. After dropwise addition of a second equivalent of H_2O_2, the mixture was stirred at 70 ℃ for another 24 hours. The solvent was then removed, and the remainder was neutralized with saturated aqueous $NaHCO_3$. Recrystallization from water afforded the product as the hemihydrate as yellow needles (5 g, 76%). ^{1}H NMR (400 MHz, D_2O): δ 8.32 (d, J =

6.9 Hz, 4H), 7.86 (d, J = 6.9 Hz, 4H). ^{13}C NMR (100 MHz, D_2O): δ 142.0, 140.4, 127.2.

1,1'-Dimethoxy-4,4'-bipyridinium bis[tetrafluoroborate]: Following the literature procedure[3], trimethyloxonium tetrafluoroborate (847 mg, 5.70 mmol) and 4,4'-dipyridyl 1,1'-dioxide (511 mg, 2.49 mmol) were stirred in 10 mL of acetonitrile for 4 hours. Recrystallization from acetonitrile afforded the product (620 mg 65%) as colorless prisms. ^{1}H NMR(400 MHz, D_2O): δ 9.34 (d, J = 7.0 Hz, 4H), 8.55 (d, J = 7.0 Hz, 4H), 4.45 (s, 6H). ^{13}C NMR (100 MHz, D_2O): δ 151.7, 143.9, 130.9, 72.3.

Control Experiments

Entry 3 Hydrolysis

1. 1,1'-Bis(2-ethoxy-2-oxoethyl)-4,4'-bipyridinium dibromide (9.8 mg, 0.02 mmol) was dissolved in 5 mL of sulfuric acid (pH = 3.0, solvent: D_2O), and the resulting mixture was gently refluxed for one hour. An aliquot of the resulting mixture was examined by ^{1}H NMR. The spectrum showed that less than 5% hydrolysis product was formed.

2. The viologen substrate (9.8 mg, 0.02 mmol) was dissolved in 5 mL of hydrochloric acid (pH = 2.3, solvent: D_2O), and the resulting mixture was gently refluxed for one hour. An aliquot of the resulting mixture was examined by ^{1}H NMR. A similar spectrum was obtained.

3. The viologen substrate (9.8 mg, 0.02 mmol) and Hcy (11.5 mg, 0.085mmol) were dissolved in 5 ml of citric acid and Na_2HPO_4 buffer (pH = 3.8, solvent: D_2O), and the resulting mixture was gently refluxed for one hour. An aliquot of the resulting mixture was examined by ^{1}H NMR. A similar spectrum was obtained except for the extra Hcy and citric acid peaks.

Dimethoxyviologen control experiment

1. The substrate dimethoxyviologen (7.8 mg, 0.02 mmol) was dissolved in 5 ml of sodium hydroxide solution (pH = 11.0, solvent: D_2O), and the resulting mixture was

gently refluxed for one hour. An aliquot of the resulting mixture was examined by ^{1}H NMR. The spectrum indicated complete consumption of dimethoxyviologen.

2. The substrate dimethoxyviologen (7.8 mg, 0.02 mmol) and Hcy (11.5 mg, 0.085 mmol) were dissolved in 5 ml of sodium hydroxide solution (pH = 11.0, solvent: D_2O), and the resulting mixture was gently refluxed for one hour. An aliquot of the resulting mixture was examined by ^{1}H NMR. The spectrum indicated complete consumption of dimethoxyviologen.

3. The substrate dimethoxyviologen (40 mg, 0.10 mmol) was dissolved in 5 ml of the buffer solution (pH = 11.0, components: NaOH + $NaHCO_3$), and the resulting mixture was gently refluxed for one hour. After cooling to room temperature, the mixture was extracted with chloroform (3 × 5 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated to give 4,4'-bipyridine (13.0 mg, 82%) as the major product. ^{1}H NMR(400 MHz, $CDCl_3$): δ 8.74 (d, J = 6.1 Hz, 4H), 7.53 (d, J = 6.1 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.7, 145.5, 121.4.

4. The substrate dimethoxyviologen (16 mg, 0.04 mmol) and Hcy (23 mg, 0.17 mmol) were dissolved in 10 ml of the buffer solution (pH = 11.0, component: NaOH + $NaHCO_3$), and the resulting mixture was gently refluxed for one hour. After cooling to room temperature, the mixture was extracted with chloroform (3 × 10 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated to give 4,4'-bipyridine (5.4 mg, 85%) as the major product.

References:

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