Supplementary Material (ESI) for Chemical Communications

Sequence Dependence of Methylation Rate Enhancement in *m*-Phenyleneethynylene Foldamers

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Supporting Information

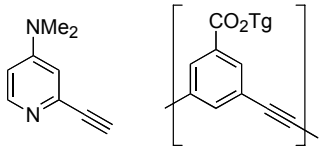
Table of Contents

General Procedures

All carbon and proton NMR spectra were obtained using either a Varian 400 or 500 MHz NMR spectrometer. All starting materials were purchased from commercial sources unless otherwise noted. Mass spectrometry was performed by the University of Illinois MicroAnalytical services. MALDI mass spectra of oligomers **2** and **9** were carried out using the HABA matrix (2-(4-hydroxyphenylazo)benzoic acid). Oligomer fragments **8** and **10** were synthesized using an iterative solid-phase method developed previously by our group.[1] Flash chromatography was performed using 60 Å silica gel from Silicycle, Inc. Analytical gel permeation chromatography (GPC) was performed using a Waters 515 HPLC pump, a Thermo Separation Products Spectraseries AS100 autosampler, a Viscotek TDA Model 300 triple detector array, and a series of three Viscotek Viscogel columns (7.8 x 300 mm, 2 GMHXL16141 and 1 G3000HXL16136 columns) with 89:10:1 THF:MeOH:NEt_3 as the eluant. The analytical GPC was calibrated using monodisperse polystyrene standards. Preparatory GPC was carried out using a Waters 515 HPLC pump, a Waters 410 Differential Diffractometer, and a series of three Waters columns (19 x 300 mm, Ultrastyragel 104 Å THF, 103 Å THF, and 500 Å THF columns) with THF (HPLC grade, inhibitor-free) as the eluant.

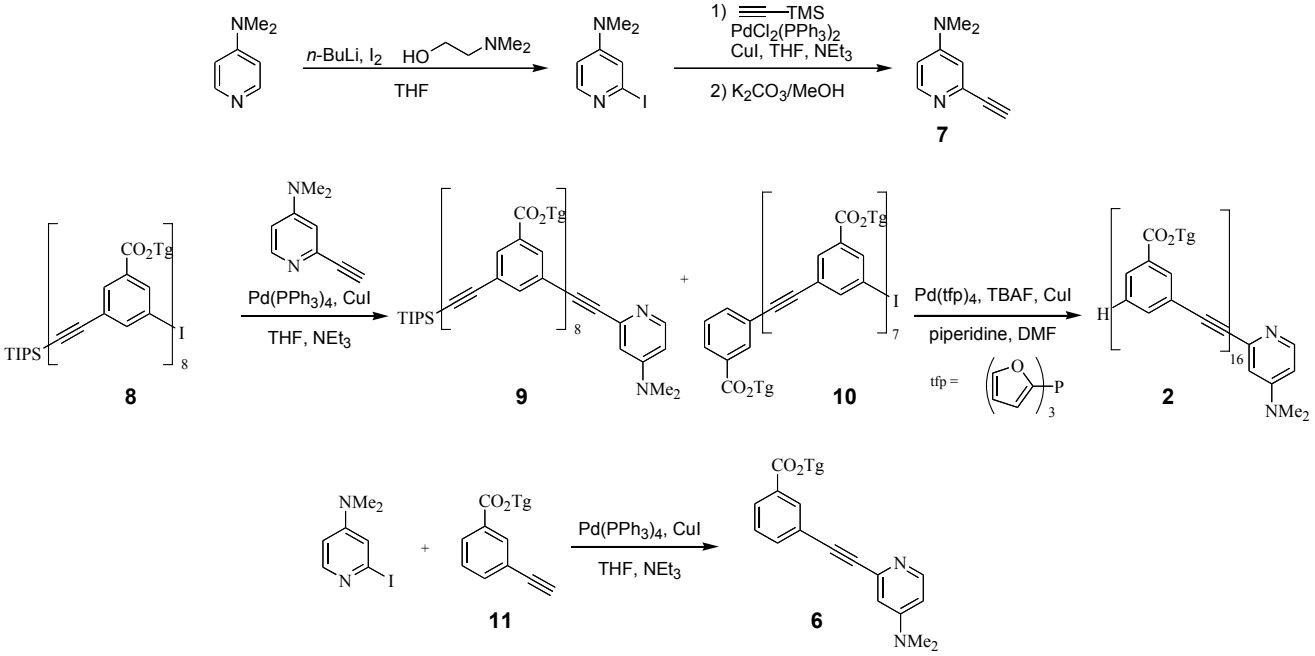
Oligomer Nomenclature

Oligomer names are defined generally as such: **D[A]$_x$**. **H** is the backbone monomer type, and **D** is the DMAP unit. The subscript **x** is the number of repeat units. Monomers are shown below.

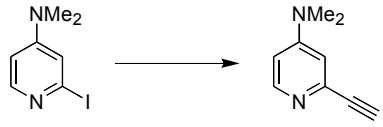


D **H**

Synthesis of Oligomers



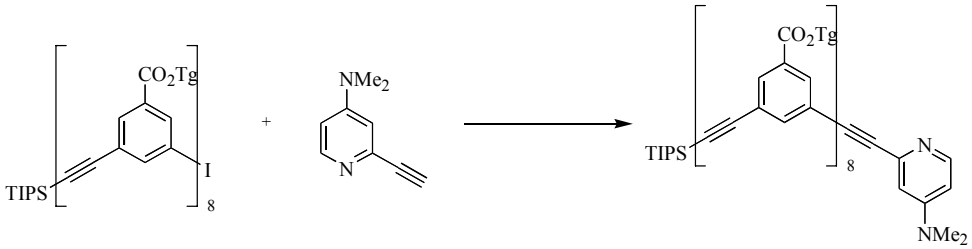
Experimental Procedures



4-(N,N-dimethylamino)-2-ethynyl-pyridine (**7**)

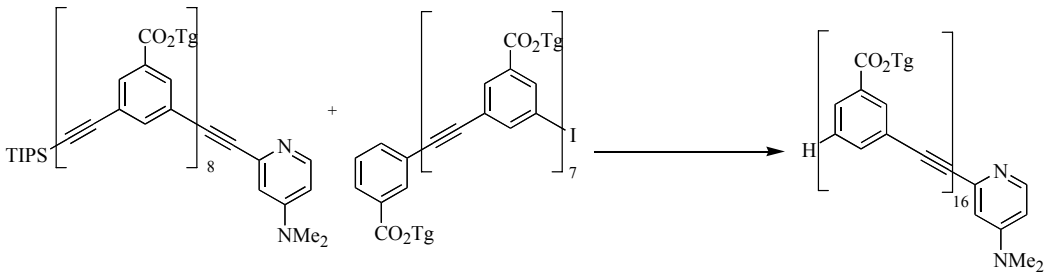
To a round bottom flask was added 2-iodo DMAP[2] (560 mg, 2.3 mmol), bis(triphenylphosphine)palladium(II)dichloride (81 mg, 0.12 mmol), and copper(I)iodide (22 mg, 0.12 mmol). The flask was purged with nitrogen for 10 min and a solution of trimethylsilylacetylene (0.6 mL, 4 mmol) in triethylamine (10 mL) was added. The reaction was stirred at room temperature for 25 min. The precipitate that formed was removed by vacuum filtration and the solvent was removed *in vacuo*. The crude material was dissolved in methanol (20 mL), and potassium carbonate (2.3 g) was added. The slurry was stirred at room temperature for 20 min, then extracted with chloroform (3 x 50 mL) from de-ionized water. The organics were dried with magnesium sulfate and filtered *in vacuo*. The brown oil obtained was purified using column chromatography (80:20 EtOAc:Hex → 100% EtOAc).

Yield = 150 mg (45%) of a light-brown solid. ^{1}H-NMR(500 MHz, $CDCl_3$) δ 3.03 (s, 6H), 3.04 (s, 1H), 6.48 (dd, 1H, J = 2.7 Hz), 6.75 (d, 1H, J = 2.7 Hz), 8.75 (d, 1H, J = 5.7 Hz). ^{13}C-NMR (500 MHz, $CDCl_3$) δ 39.33, 75.41, 84.06, 106.62, 110.59, 142.35, 150.15, 154.41. HR-MS(ESI) = *m/z* 147.0920 (calc'd 147.0922). MP = 73-74^0 C.



D[H]$_8$ **(9)**

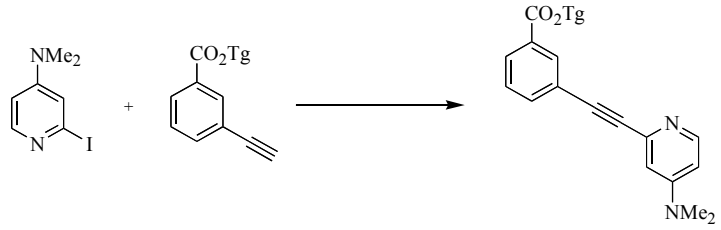
General Procedure A. To a 20 mL scintillation vial containing 8-mer **8** (70 mg, 0.027 mmol) was added palladium (0) tetrakis(triphenylphosphine) (3.1 mg, 0.0027 mmol), copper(I)iodide (1 mg), triethylamine (0.5 mL), and tetrahydrofuran (1.5 mL) and **7** (5.8 mg, 0.04 mmol) under an argon atmosphere. The reaction was stirred overnight at rt. The solvents were removed *in vacuo* and the crude wax was purified by preparative GPC in THF (retention time 17 min at 7 mL/min flow rate). Yield = 53 mg (75%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.13 (s, 21H), 3.04 (s, 6H), 3.34 (s, 24H), 3.53 (m, 16H), 3.64-3.73 (m, 48H), 3.87 (m, 16H), 4.52 (m, 16H), 6.47 (m, 1H), 6.81 (m, 1H), 7.81-8.26 (m, 25H). MS(MALDI): *m/z* 2624.80 (calc'd 2625.02).



D[H]$_{16}$ **(2)**

Oligomer **8** (36 mg, 0.015 mmol) was placed in a 20 mL scintillation vial under an argon atmosphere and dissolved in DMF (1.0 mL). TBAF (25 µL, 1.0 M solution in THF) was then added followed by palladium tetrakis(trifurylphosphine)[1] (2.0 mg, 1.8 µmol), copper (I) iodide (1.0 mg, 5.3 µmol), piperidine (50 µL) and finally oligomer **9** (31 mg, 0.012 mmol). This reaction was stirred overnight at rt. The solvents were removed *in vacuo* and the dark brown waxy material was purified by preparative

GPC in THF. Yield = 18 mg (32%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 3.05 (s, 6H), 3.35 (s, 48H), 3.53-3.55 (m, 32H), 3.65-3.75 (m, 96H), 3.88 (m, 32H), 4.54 (m, 32H), 6.48 (m, 1H), 6.81 (m, 1H), 7.45-8.26 (m, 49H). GPC: PDI = 1.07. MS(MALDI): *m/z* 4766.60 (calc'd 4767.15)



D[H]$_1$ **(6)**

2-iodo DMAP (120 mg, 0.48 mmol) and **11** (234 mg, 0.8 mmol) were reacted according to **General Procedure A.** This compound was purified by column chromatography (100% EtOAc → 90:10 EtOAc:NEt_3). Yield: 185 mg (93%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 3.01 (s, 6H), 3.33 (s, 3H), 3.51 (m, 2H), 3.62-3.71 (m, 6H), 3.82 (m, 2H), 4.46 (m, 2H), 6.44 (dd, 1H, J = 2.6 Hz), 6.77 (d, 1H, J = 2.6 Hz), 7.41 (t, 1H, J = 7.7 Hz), 7.74 (d, 1H, J = 7.9 Hz), 8.01 (d, 1H, J = 7.9 Hz), 8.19 (d, 1H, J = 6.0 Hz), 8.26 (s, 1H). ^{13}C-NMR (500 MHz, $CDCl_3$) δ 39.37, 59.23, 64.56, 69.33, 70.79, 70.81, 70.89, 72.09, 86.37, 90.69, 106.34, 110.35, 123.32, 128.73, 129.97, 130.61, 133.41, 136.35, 142.99, 150.17, 154.45, 166.05. HR-MS(ESI) = *m/z* 413.2073 (calc'd 413.2076).

UV Kinetics Experiments

UV experiments were performed using a Shimadzu UV-2401PC spectrophotometer using 1 cm, 1.5 mL quartz cells equipped with a temperature controlled cell holder set at 25 ^{0}C. Methylation kinetics data of **2** and **6** were obtained at wavelengths of 360 nm and 340 nm respectively. Stock solutions of host molecule (**2** or **6**) were prepared by dissolving the desired amount of material in acetonitrile using a volumetric flask. A stock solution of **2** in acetonitrile was diluted to ca. 3.5-4 μM **(**13 μM in the case of **6** due to lower absorptivity**)** and placed in a UV cell. The methylating agent was then added neat or as a stock solution in acetonitrile. Absorbance data were plotted as $(\ln[M_o]/[M])/[MeX]$ vs. time ($[M_o]$ = initial conc. of oligomer, [M] = conc. of oligomer at each measurement). The second order rate constant was obtained as the slope.[3, 4] All of the experiments were performed in triplicate and error is reported as the standard deviation of the values. Shown below are some sample UV traces and $\ln[M_o]/[M])/[MeX]$ vs. time plots (Figures 1 and 2). Sample plots are from methylations of **2**.

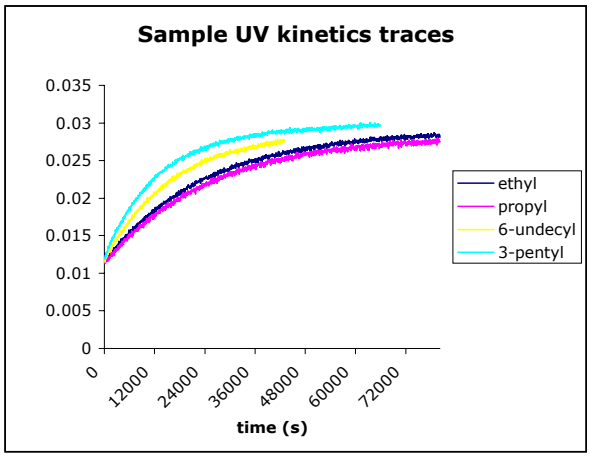


Figure 1. Raw UV/Vis kinetics traces.

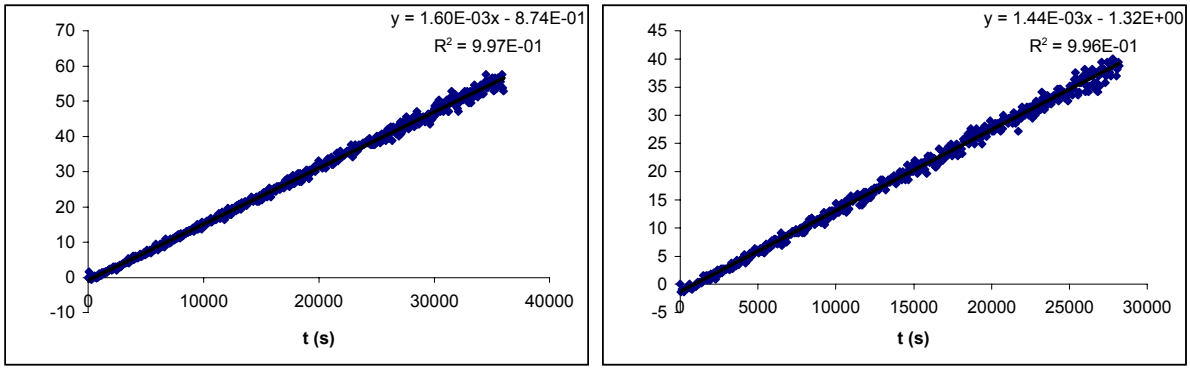


Figure 2. Sample ln[M_o]/[M])/[MeX] vs. time plots for ethyl methanesulfonate **3b** (left) and propyl methanesulfonate **3c** (right). The slope of the fitted line was taken as the second order rate constant (k_2).

Rate Coefficients (k_2) for Kinetics Experiments

Linear Series	k_2 x 10^{-3}	**Branched Series**	k_2 x 10^{-3}	**Controls**	k_2 x 10^{-3}
Methyl (**3a**)	1.40 ± 0.04	2-butyl (**4a**)	2.07 ± 0.10	Trimer (**5**)	0.025 ± 0.002
Ethyl (**3b**)	1.60 ± 0.21	3-pentyl (**4b**)	3.45 ± 0.11	Dimer (**6**)	0.63 ± 0.03
Propyl (**3c**)	1.70 ± 0.21	4-heptyl (**4c**)	2.64 ± 0.11		
Butyl (**3d**)	2.56 ± 0.05	5-nonyl (**4d**)	2.40 ± 0.13		
Heptyl (**3e**)	4.58 ± 0.36	6-undecyl (**4e**)	2.85 ± 0.20		
Octyl (**3f**)	7.82 ± 0.68				
Decyl (**3g**)	7.91 ± 0.55				
Undecyl (**3h**)	12.3 ± 1.30				

The rate coefficients for the linear and branched series methylating agents are for oligomer **2**. Rate coefficients for oligomer **1** are reported in our previous work.[4]

References

1. E. L. Elliott, C. R. Ray, S. Kraft, J. R. Atkins and J. S. Moore, *J. Org. Chem.*, 2006, **71**, 5282-5290.
2. D. Cuperly, P. Gros and Y. Fort, *J. Org, Chem.*, 2002, **67**, 238-241.
3. J. M. Heemstra and J. S. Moore, *J. Am. Chem. Soc.*, 2004, **126**, 1648-1649.
4. R. A. Smaldone and J. S. Moore, *J. Am. Chem. Soc.*, 2007, **129**, 5444-5450.