Supporting Information

Efficient Isonitrile Hydration through Encapsulation within a Hexameric Self Assembled Capsule and Selective Inhibition by a Photo-Modulable Competitive Guest

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General

^{1}H-NMR, ^{13}C{^{1}H}-NMR and ^{31}P{^{1}H}-NMR were recorded at 298 K with a BRUKER AVANCE spectrometer operating respectively at 300.15, 75 and 121.5 MHz, respectively.

GC analysis were performed on HP SERIES II 5890 equipped with a HP5 column (30 m, I. D. 0.25 m, film 0.25 μm) using He as gas carrier and FID. GC-MS analyses were performed on a GC Trace GC 2000 equipped with a HP5-MS column (30 m, I.D. 0.25 mm, film 0.25 μm) using He gas carrier and coupled with a quadrupole MS Thermo Finnigan Trace MS with *Full Scan* method.

Solvents and reactants were used as received; otherwise they were purified as reported in the literature.[1] Product identification was accomplished by reference samples or by comparison with samples obtained as described in the literature for species **2a**,[2] **2b**,[3] **2c** and **2d**,[4] **2e**.[5]

TLC analysis were performed on TLC Polygram ® Sil G/UV254 of 0.25 mm thickness and flash-chromatography separations were performed on silica gel Merk 60, 230-400 mesh.[6]

Compounds 1,2-bis(5-chloro-2-methylthiophen-3-yl)cyclopent-1-ene, 1,2-*bis*(2-methyl-5-(pyridin-4-yl)thiophen-3-yl)cyclopent-1-ene) **6**, open 4,4'-(4,4'-(cyclopent-1-ene-1,2-diyl)bis(5-methylthiophene-4,2-diyl))bis(1-methylpyridin-1-ium) bis(trifluoromethanesulfonate) **5o** and closed 4,4'-(4,4'-(cyclopent-1-ene-1,2-diyl)bis(5-methylthiophene-4,2-diyl))bis(1-methylpyridin-1-ium) bis(trifluoromethanesulfonate) **5c** were prepared as reported in the literature[7] while resorcin[4]arene **3** was prepared according to reported procedure.[8]

Irradiation at 365 nm was performed with a Wood lamp, omnilux 25 W, irradiance at 365 nm 10 W/m^{2} (10 cm) while irradiation in the visible region was performed with a visible light lamp (120 W).

Table S1. Catalytic tests for the hydration of **1a** mediated by **3**.

#	$\mathbf{3}_6$	4	**2a** (%)[a]
1	-	-	0
2	+	-	>98
3	+	+	<5
4	-	+	0
5[b]	-	-	<5

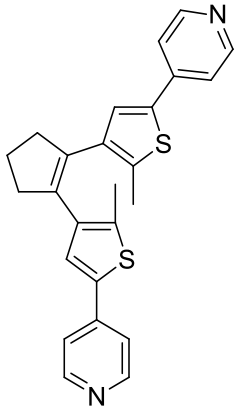
[**1a**]= 60 mM, [**3**]= 36 mM, [**4**]= 60 mM (10 eq. with respect to the capsule), water saturated chloroform-d 0.5 mL, T=60°C, time 18h. +: presence; -: absence; a) Determined by GC; b) [resorcinol] = 144 mM (4 eq. with respect to **3**).

Table S2. Catalytic tests for the hydration of **1a-b** mediated by $\mathbf{3}_6 \cdot 8H_2O$ in the presence of competitive photo-modulable guests **5o** and **5c**.

#	Substrate	Inhibitor	**2a** (%)[a]	
1	**1a**	**5o**	10[b]	
2	**1a**	**5c**	33[b]	
3	**1a**	**5o**	33	
4	**1a**	**5c**	68	
5	**1b**	**5o**	15[c,d]	
6	**1b**	**5c**	26[c,d]	
7	**1b**	**5o**	50[d]	38[d,e]
8	**1b**	**5c**	59[d]	67[d,e]

[**1a-c**]= 60 mM, [**3**]= 36 mM, [**5o** or **5c**]= 6 mM, water saturated chloroform-d 0.5 mL, T=60°C, 18h. a) Determined by GC; b) 3h; c) 2h; d) determined by ^{1}H-NMR. e) Room temperature for 7 days.

*Synthesis of 1,2-bis(2-methyl-5-(pyridin-4-yl)thiophen-3-yl)cyclopent-1-ene (**6**)*



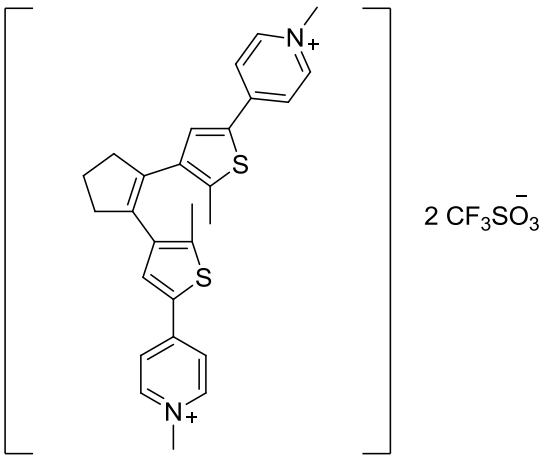
The synthesis of this product is divided in two parts. *Part A* concerns the preparation of THF solution of a thiophene-borate reactant bearing the dithyenilethene moiety suitable for the Suzuki cross coupling. *Part B* reports the cross-coupling reaction.

Part A. A two necks round bottom flask equipped with a rubber septum and connected to a vacuum/nitrogen line was flame dried and three vacuum/nitrogen cycles performed. Subsequently under nitrogen atmosphere 1,2-bis(5-chloro-2-methylthiophen-3-yl)cyclopent-1-ene (1.88 g, 0.0057 mol) and dry THF (15 mL) were added. The resulting mixture was cooled to 0°C with an ice bath and *n*-BuLi (2.5 M, 5.04 mL, 0.0126 mol) was slowly added with a syringe. During the addition the mixture turned dark grey and upon completion of the addition it was stirred for further 15 min at the same temperature. Subsequently *tris*-*n*-butylborate (3.94 g, 4.62 mL, 0.0171 mol) was added in one portion with a syringe and the resulted orange solution was allowed to warm up to room temperature and stirred for 1h.

Part B. To a two necks round bottom flask equipped with a condenser, THF (20 mL) and $Pd(PPh_3)_4$ (0.370 g, $3.2 \cdot 10^{-4}$ mol) were added and the resulting solution heated at 70°C. After 15 min at this temperature, aqueous K_2CO_3 (2 M, 25 mL, 0.05 mol), ethylene glycol (10 drops), 4-bromopyridine hydrochloride (2.43 g, 0.00125 mol) were added and, to the well stirred solution at the same temperature, the THF solution containing the borate prepared in *Part A* was slowly added with a syringe. The mixture was left at 70°C for 16h further cooled to room temperature followed by addition of water (20 mL) and product extraction with diethyl ether (3x50 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The product was obtained as a light violet solid in 62% yield.

^{1}H-NMR (300.15 MHz, $CDCl_3$): δ 2.02 (3, 6H), 2.11 (q, J=7.5 Hz, 2H), 2.85 (t, J=7.5 Hz, 4H), 7.21 (s, 2H), 7.34 (dd, J=4.6 and 1.7 Hz, 4H), 8.53 (dd, J=4.6 and 1.7 Hz, 4H)
^{13}C-NMR (75 MHz, $CDCl_3$): δ 14.64, 22.98, 38.45, 119.24, 126.27, 134.79, 136.65, 137.07, 137.26, 141.27, 150.24.

*Synthesis of open isomer 4,4'-(4,4'-(cyclopent-1-ene-1,2-diyl)bis(5-methylthiophene-4,2-diyl))bis(1-methylpyridin-1-ium) bis(trifluoromethanesulfonate) (**5o**)*

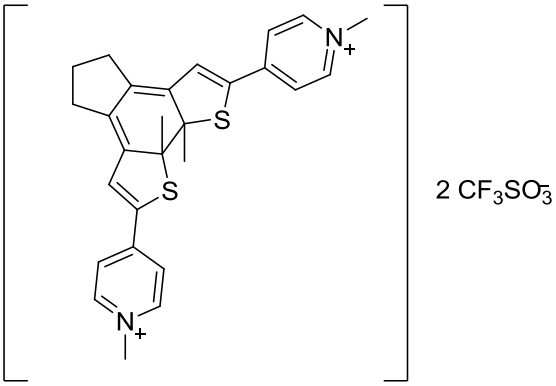


A two necks round bottom flask connected to a vacuum/nitrogen line was flame dried and three vacuum/nitrogen cycles were performed, subsequently under nitrogen atmosphere **6** (0.47 g, 0.0011 mol) and dry dichloromethane (20 mL) were added. To the well stirred solution methyl trifluoromethanesulfonate (0.54 g, 0.37 mL, 0.0033 mol) was then added with a syringe and immediately the light violet solution turned greenish. The mixture was stirred for further 16h. The solvent and the un-reacted methyl triflate were removed under vacuum and the product isolated in quantitative yield was not further purified.

^{1}H-NMR (300.15 MHz, CD_3CN): δ 2.11 (s, 6H), 2.13 (q, J=7.4 Hz, 2H), 2.88 (t, J=7.4 Hz, 4H), 4.17 (s, 6H), 7.78 (s, 2H), 7.94 (d, J=6.8 Hz, 4H), 8.44 (d, J=6.8 Hz, 4H)
^{1}H-NMR (300.15 MHz, D_2O): δ 1.93 (s, 3H), 2.01 (q, J=7.4 Hz, 2H), 2.76 (t, J=7.4 Hz, 4H), 4.11 (s, 6H), 7.70 (s, 2H), 7.84 (d, J=7.1 Hz, 4H), 8.39 (d, J=7.1 Hz, 4H)

^{13}C-NMR (75 MHz, CD_3CN): δ 13.40, 14.24, 38.07, 47.03, 121.58, 132.94, 132.99, 135.11, 138.91, 144.65, 144.93, 148.49; (12 of 13 found)

*Synthesis of closed isomer 4,4'-(4,4'-(cyclopent-1-ene-1,2-diyl)bis(5-methylthiophene-4,2-diyl))bis(1-methylpyridin-1-ium) bis(trifluoromethanesulfonate) (**5c**)*



5o (0.003 g, $4.04 \cdot 10^{-6}$ mol) and the desired deuterated solvent (0.65 mL) were loaded in a NMR tube. The resulting solution was irradiated with a Wood lamp until the ring closing reaction was complete (about 5 min) as confirmed by acquisition of the ^{1}H NMR spectrum. During the irradiation the sample became dark green.

^{1}H-NMR (300.15 MHz, D_2O): δ 1.86 (q, J=7.2 Hz, 2H), 1.97 (s, 6H), 2.53 (t, J=7.2 Hz, 4H), 4.18 (s, 6H), 7.19 (s, 2H), 7.83 (d, J=6.2 Hz, 4H), 8.48 (d, J=6.2 Hz, 4H)

*Typical procedure for isonitrile hydration reaction in presence of **5o***

In a 1.5 mL vial were introduced a water saturated chloroform solution of **3** (36 mM, 0.5 mL) and **5o** (1 eq. with respect to $\mathbf{3}_6 \cdot 8H_2O$, 0.003 mmol, 2.3 mg) and the resulted mixture vigorously stirred until completely homogeneous. Subsequently the desired isonitrile was added (10 eq. with respect to $\mathbf{3}_6 \cdot 8H_2O$, 0.030 mmol), the vial sealed and thermostatted at 60°C. The reaction progression was followed by GC or ^{1}H-NMR analyses sampling the reaction mixture at different times.

*Typical procedure for isonitrile hydration reaction in presence of **5c***

5o (0.003 mmol, 2.3 mg) was photoisomerized to **5c** in an acetonitrile solution as previously described. After solvent removal at reduced pressure, a water saturated chloroform solution of **3** (36 mM, 0.5 mL) was added and the system stirred until completely homogeneous. Subsequently the desired isonitrile was added (10 eq. with respect to $\mathbf{3}_6 \cdot \mathbf{8H_2O}$, 0.030 mmol) and the obtained solution transferred in a 1.5 mL vial which was in turn sealed and thermostatted at 60 °C. The reaction progression was followed by GC or ^{1}H-NMR analyses sampling the reaction mixture at different times.

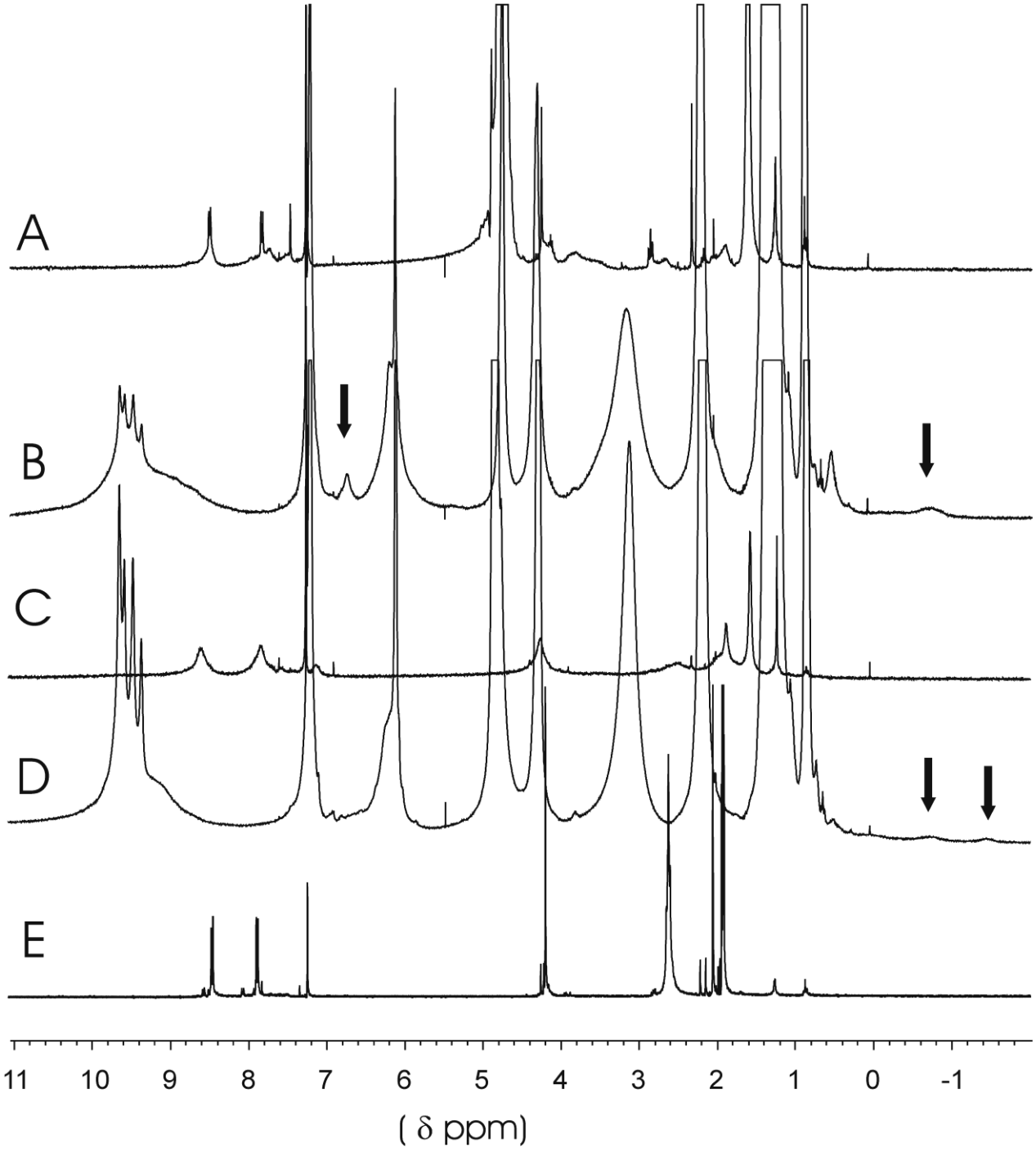


Figure S1. A) free open cation **5o** (6 mM) in water saturated chloroform-d; B) **5o** open *bis*-cation(6 mM) and **3** (36 mM); C) **5c** closed *bis*-cation (6 mM); D) **5c** (6 mM) and **3** (36 mM); E) **5c** closed *bis*-cation (6 mM in acetonitrile-d_3); ↓ encapsulated inhibitor.

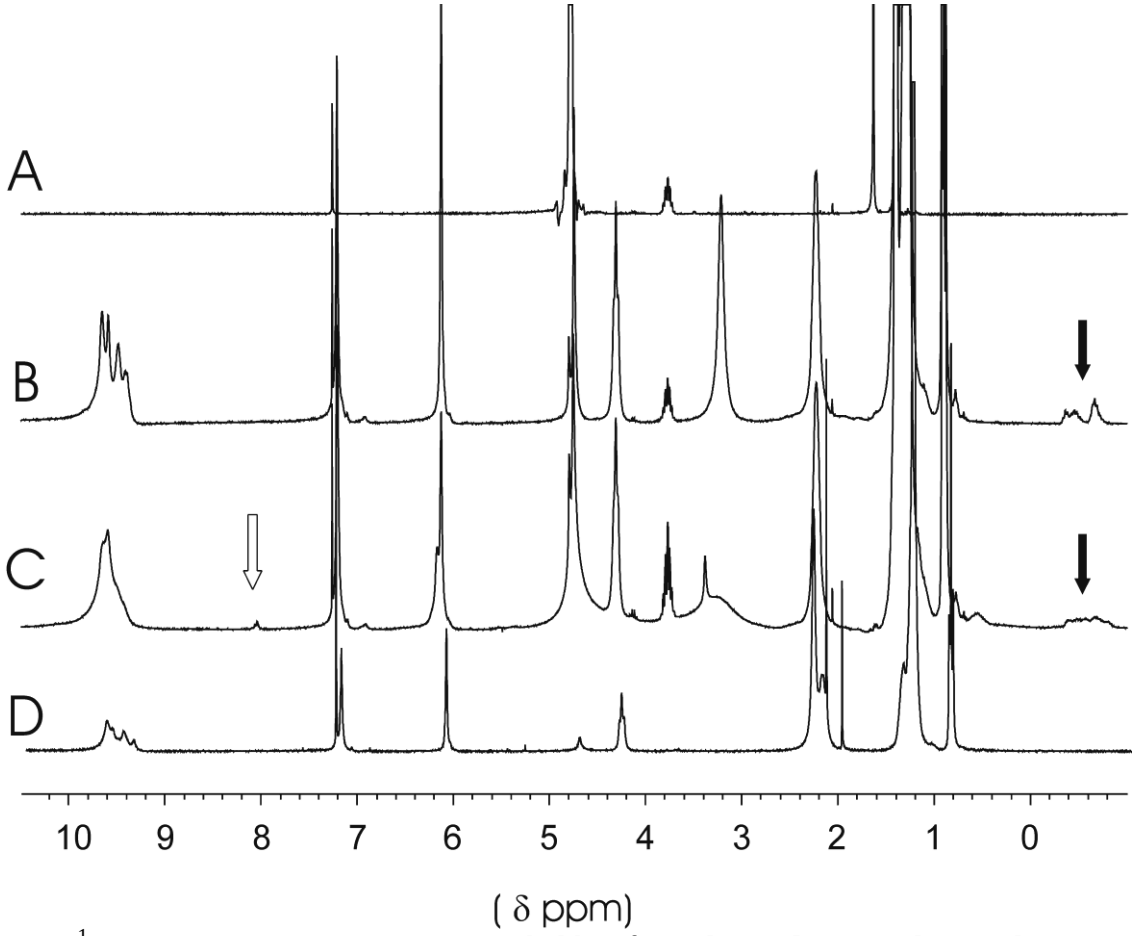


Figure S2. ^{1}H NMR spectra in water saturated chloroform-d: A) **1b** *i*-propylisonitrile (60 mM); B) **1b** (60 mM) and **3** (36 mM); C) **1b** (120 mM) and **3** (36 mM); D) **3** (36 mM). ⬇ encapsulated substrate, ⇩ *N*-formylamide product.

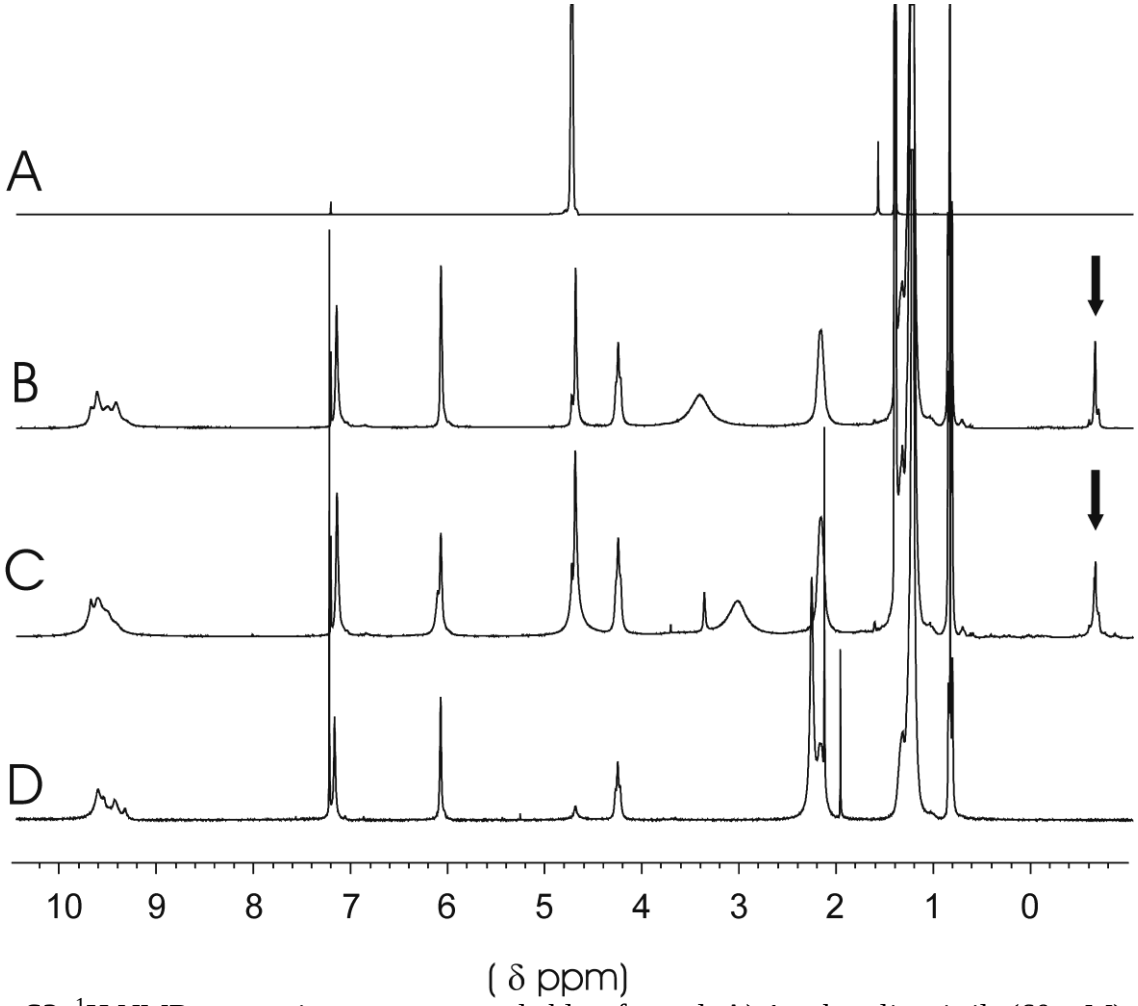


Figure S3. ^{1}H NMR spectra in water saturated chloroform-d: A) **1c** *t*-butylisonitrile (60 mM); B) **1c** (60 mM) and **3** (36 mM); C) **1c** (120 mM) and **3** (36 mM); D) **3** (36 mM). ↓ encapsulated substrate.

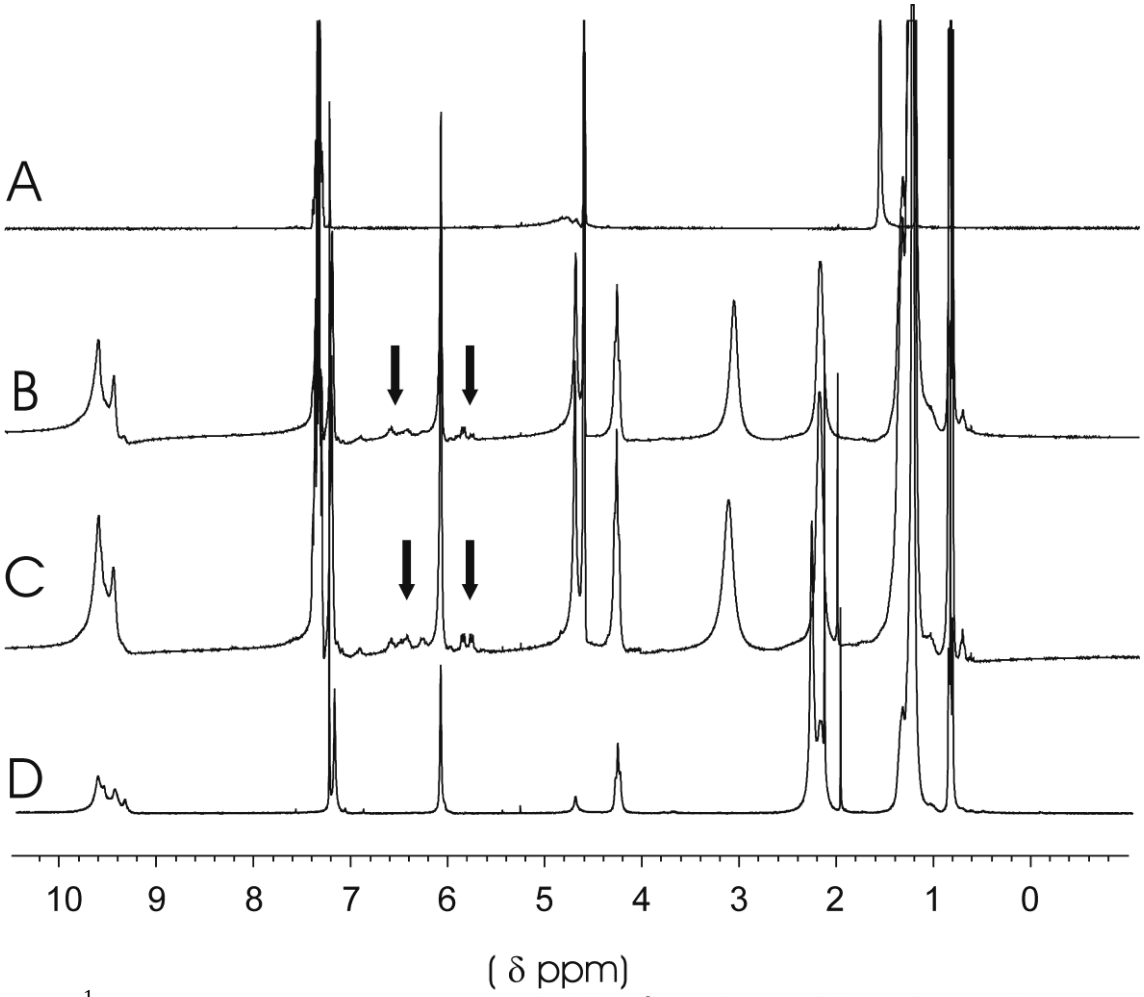


Figure S4. ^{1}H NMR spectra in water saturated chloroform-d: A) **1d** benzylisonitrile (60 mM); B) **1d** (60 mM) and **3** (36 mM); C) **1d** (120 mM) and **3** (36 mM); D) **3** (36 mM). ⬇ encapsulated substrate, ⇩ *N*-formylamide product.

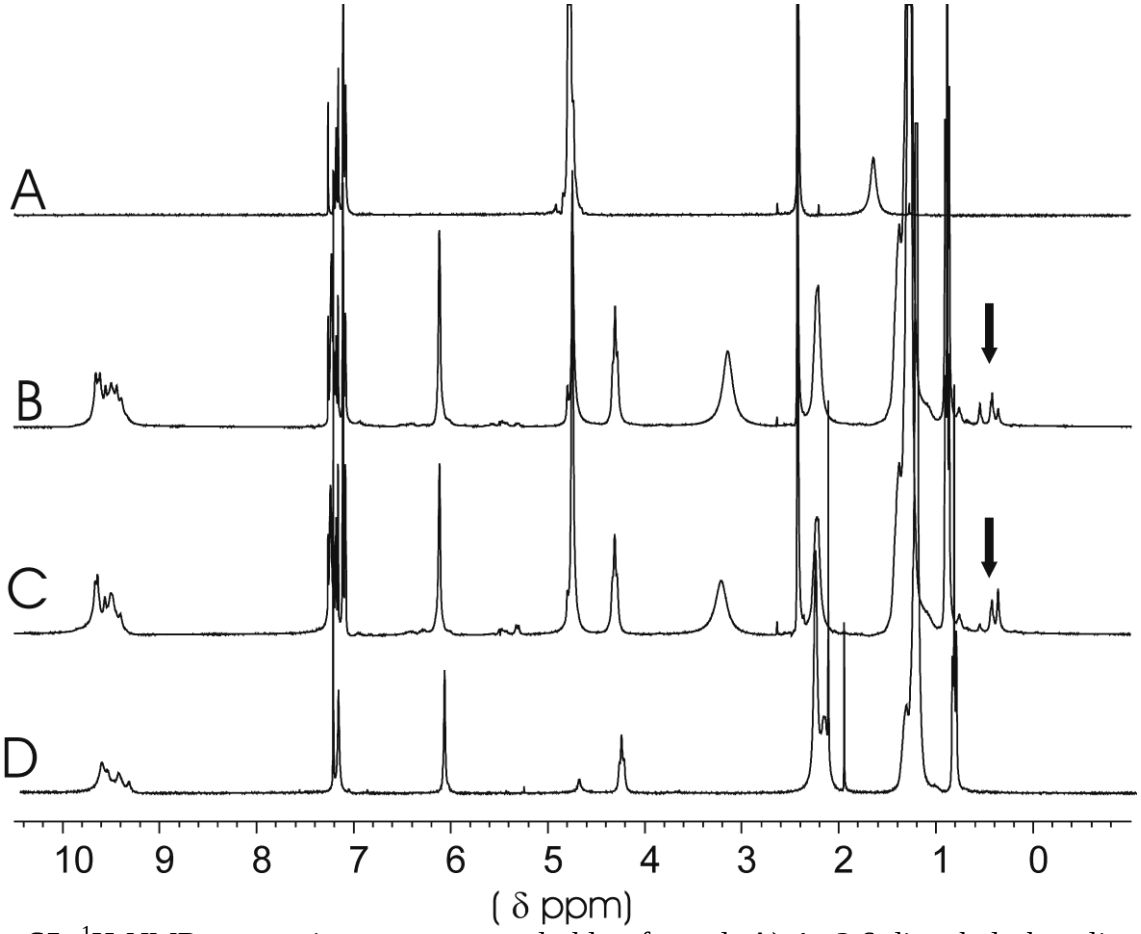


Figure S5. ^{1}H NMR spectra in water saturated chloroform-d: A) **1e** 2,6-dimethyl-phenylisonitrile (60 mM); B) **1e** (60 mM) and **3** (36 mM); C) **1e** (120 mM) and **3** (36 mM); D) **3** (36 mM). ↓ encapsulated substrate.

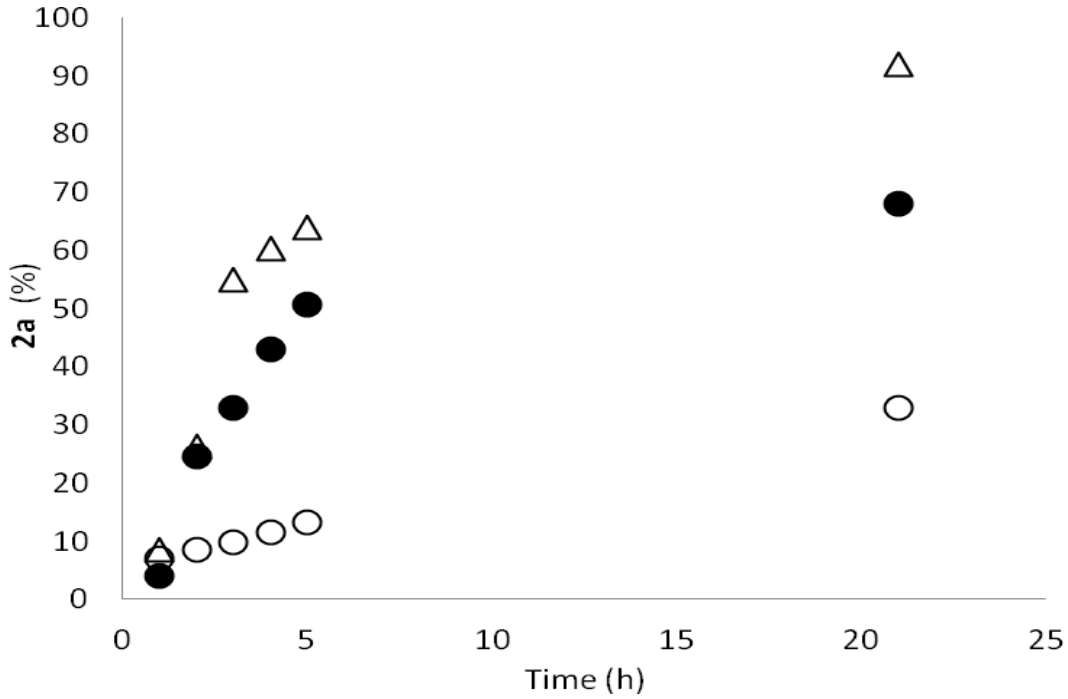


Figure S6. Hydration of **1a** to **2a** in water saturated chloroform-d (0.5 mL) at 60°C in the presence of a) free $\mathbf{3}_6{\cdot}8H_2O$ (Δ); b) $\mathbf{3}_6{\cdot}8H_2O$ with **5o** (o); c) $\mathbf{3}_6{\cdot}8H_2O$ with **5c** (•). **3** (36 mM), **1a** (60 mM) and **5o** or **5c** (6 mM).

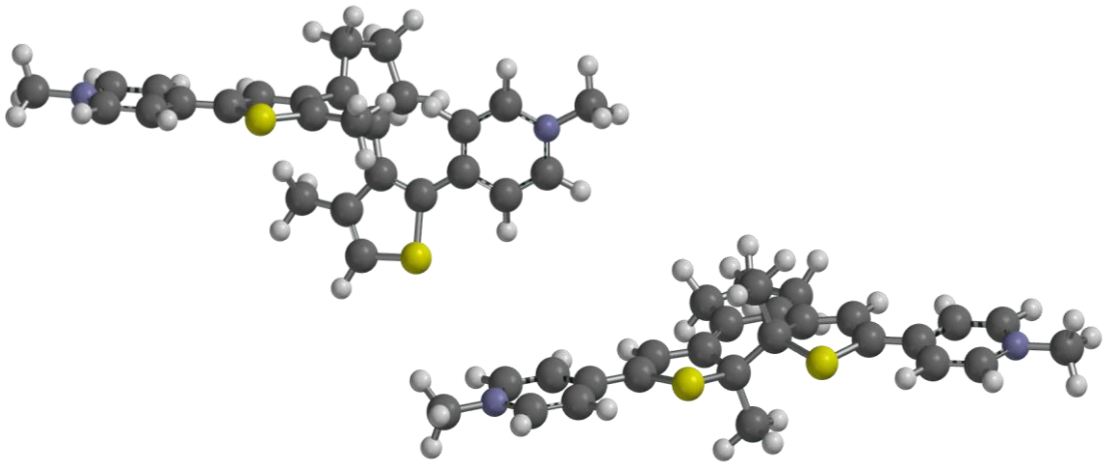


Figure S7. Open, top, and closed, bottom, bis-pyridinium ion **5o** and **5c**.

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