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Observation of Electrochemically Controlled Quantum Interference in a Single Anthraquinone-based Norbornylogous Bridge Molecule

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There is considerable ongoing interest in understanding the electrical properties of single molecules both from a fundamental point of view and for potential applications in single-molecule technologies.[1-4] An important goal in molecular electronics is the ability to switch, by means of electrochemical gating, the conductance through a single molecule and, in this context, the anthraquinone/hydroanthraquinone, AQ/H_2AQ, redox couple has been proposed as a suitable candidate for study.[5] Indeed, calculations[6] predict that electrochemical gating of conductance in AQ-based molecular switches should be strong, with conductance *on*(H_2AQ)/*off*(AQ) ratios of several orders of magnitude. The switching mechanism is due to the presence of destructive quantum interference (QI) between various conductance channels in the cross-conjugated AQ, which is absent in the linear-conjugated H_2AQ, thereby resulting in lower conductance in AQ, compared to H_2AQ. Recently, Fracasso *et al.*[7] have experimentally confirmed the operation of QI in bulk conductance studies of SAMs of arylethynylene thiolates (aryl = anthracene, AQ, 9,10-dihydroanthracene).[7]

We now report the first experimental evidence for the operation of electrochemically-controlled QI in a novel AQ-based norbornylogous bridge tetrathiol, **5AQ5** (Figure 1), from single-molecule conductance measurements using the STM break junction technique.[8] We show that the AQ moiety in **5AQ5** can be electrochemically and reversibly switched *in-situ* between the high conducting H_2AQ form and the low conducting AQ system. Further, we demonstrate that the potential range of the conductance enhancement can be shifted using different pH values. This pH dependency of the AQ/H_2AQ redox reaction constitutes an extra degree of freedom that can control single molecule conductivity.

A key design feature of **5AQ5** is the cementing of the AQ group into a rigid, structurally well-defined norbornylogous (NB) unit bearing two pairs of thiol groups at each end, thereby conferring additional stability to SAMs derived therefrom. The 19.8 Å length of **5AQ5** is much greater than the gate thickness, that is the electrochemical double layer that relates to the diameter of the ions used in the electrolyte, thereby ensuring that the field screening effect due to the proximity of the source and drain electrodes is negligible.[9]

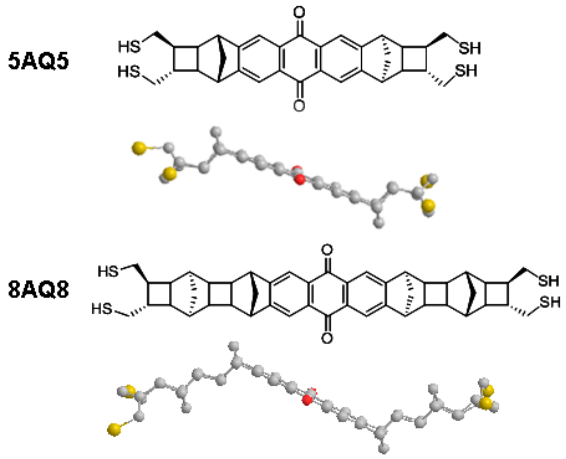

Figure 1. Molecular structure of the compounds used in this study. **5AQ5** molecule possesses 5 bonds on each side and an AQ moiety in the center. **8AQ8** possesses 8 bonds on each side and an AQ moiety in the center. The detailed experimental procedures for the synthesis of compounds **5AQ5** and **8AQ8** along with analytical and spectral information can be found in the SI.

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Norbornylogous bridges have played pivotal roles in investigating many fundamental aspects of electron transfer (ET) processes,[10, 11] including those involving SAMs derived therefrom.[12-16] In particular, NB bridges are very efficient mediators of ET by the superexchange mechanism and it was hoped that the NB bridge would likewise facilitate coherent charge transport in **5AQ5**, which is a *sine qua non* for QI to be operative. This issue was first investigated by determining the magnitude and distance dependence of single-molecule conductivity in **5AQ5** and its longer cognate, **8AQ8**. XPS and STM studies on SAMs formed from **5AQ5** and **8AQ8** on gold surfaces confirmed that that the **5AQ5** and **8AQ8** molecules stand upright on the gold surface – anchored by a pair of thiolates at one end – and a pair of free thiols at the distal end that are easily accessible to the gold STM tip (see SI). Single-molecule conductance measurements were determined using STM break junction method with a two-electrode setup.[8] Conductance histograms were built using several hundred current transient curves for **5AQ5** and **8AQ8** (see experimental section for details). The conductance values for **5AQ5** and **8AQ8** are $2.7 \times 10^{-4} \pm 1.1 \times 10^{-4}$ G_o and $1.7 \times 10^{-5} \pm 1.0 \times 10^{-5}$ G_o, respectively. These values are significantly larger than those obtained previously for completely saturated NB tetrathiolates of comparable length.[14] For example, the conductance of **5AQ5**, with a bridge length of 16 bonds, is more than two orders of magnitude greater than that measured for a completely saturated 15-bond NB bridge molecule (1.6×10^{-6} G_o).[14] The distance dependence attenuation factor[a], ß, for the conductance of **5AQ5** and **8AQ8** is 0.46 ± 0.17 $bond^{-1}$. This value is smaller than that obtained for saturated NB bridge systems (ca. 1 $bond^{-1}$).[2] The enhanced conductance and smaller ß value for **5AQ5** and **8AQ8**, compared to saturated NB bridges, signifies that the charge transport in these molecules is occurring through superexchange-mediated coherent (i.e. tunneling) charge transport involving virtual states of the AQ group. An incoherent, ohmic scattering mechanism is ruled out on the grounds that the conductance would show a linear dependence on bridge length resulting in a conductance ratio for **5AQ5:8AQ8** of ca. 1.4, instead of the observed value of 15.9.

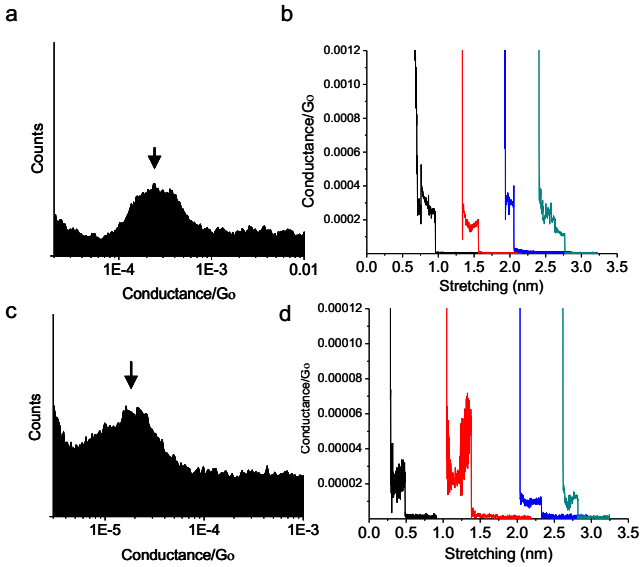

Figure 2. a) Conductance histogram of **5AQ5**. b) Typical individual current transient curves of **5AQ5**. c) Conductance histogram of **8AQ8**. d) Typical individual current transient curves of **8AQ8**. The histograms were built from ca. 750 individual transient curves by counting the number of times each step occurs and weighting that number by the time duration of the step.

Electrochemical gating of **5AQ5** was performed using a four-electrode setup in which a counter electrode, controlled through a reference electrode, acts as the "gate" for the tunneling process. The other two electrodes (the STM tip and the gold surface) act as contacts to the molecules and can be thought of as the source or the drain of a single molecular device.

The AQ moiety in **5AQ5** undergoes proton-coupled redox reaction in aqueous solutions and the redox couple can be switched between the oxidized AQ form and the reduced H_2AQ form.[17] This is confirmed using cyclic voltammograms (CVs) of a SAM formed from **5AQ5** on an Au (111) surface in 0.5 M phosphate buffer at two different pH values (pH 3 and pH 8). The CVs show reduction/reoxidation peaks corresponding to a two-electron redox switching of the AQ redox center (Figure 3a). The $E_{1/2}$ of the redox reaction was found to shift more cathodic by ca. 315 mV when the buffer used is changed from pH = 3 to pH = 8. The values of $E_{1/2}$ were obtained from the peak maximum in alternating current voltammograms (ACVs) at low frequency of 1 Hz (Figure 3b). The shift of $E_{1/2}$ with pH is consistent with a $2e^-/2H^+$ redox reaction which is widely reported on AQ SAMs in this pH range.[17-19] The anodic and the cathodic waves in the CVs scaled linearly with the scan rate indicating a surface-related redox process. Plots showing the scan rate dependence of the peak current and the peak potential are presented in the SI.

[a]Conductance is given by $G=G_c e^{-\beta L}$ where G_c is the contact conductance, ß is the tunneling decay constant, and L is the length of the molecule.

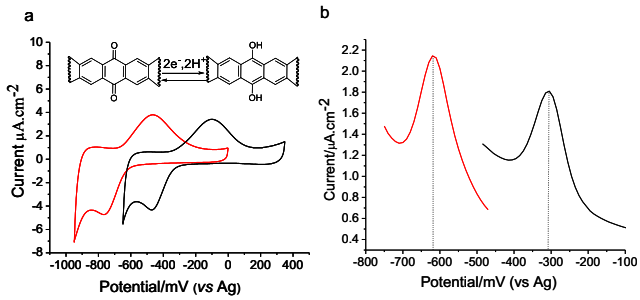

Figure 3. a) Cyclic voltammetry at 50 mV/sec *vs.* Ag of an Au (111) surface modified with a SAM of **5AQ5** in 0.5 M phosphate buffer, pH=3 (black line) and pH = 8 (red line); inset is the redox reaction of the AQ moiety to an H_2AQ moiety. b) ACVs at pH = 3 (black line) and pH=8 (red line). Data was obtained at a frequency of 1 Hz and AC amplitude of 15 mV.

Figure 4 shows the corresponding electrochemical potential dependence of the single molecule conductance of **5AQ5** at pH = 3 and pH = 8. The conductance measurements were performed at a constant tip-surface bias of +100 mV. At a surface potential of +300 mV (*vs* Ag), where the AQ is in its oxidized form, the single-molecular conductance of **5AQ5** is $2.4 \times 10^{-4} \pm 1.2 \times 10^{-4}$ G_o which is close to that obtained with the two electrode systems ($2.7 \times 10^{-4} \pm 1.1 \times 10^{-4}$ G_o).

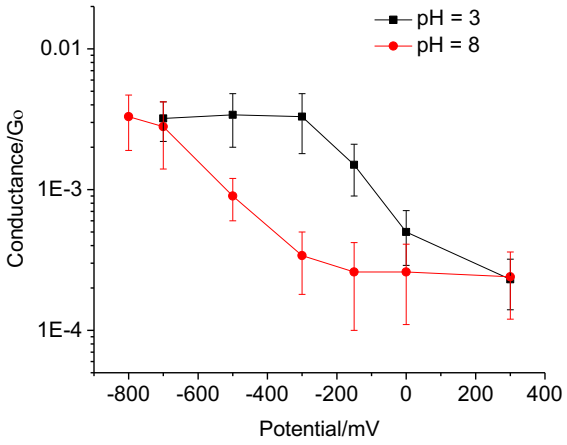

Figure 4. Evolution of the conductance of **5AQ5** with gate potential at pH=3 (black line) and pH=8 (red line). Each data point is the peak maximum in the histograms. Error bars are calculated from the fwhm of the histogram peaks. Each data point is obtained at a fixed gate potential *vs* Ag. The conductance value plateaus at ca. −300 mV for pH=3 and ca. −700 mV for pH=8. Typical individual curves along with histograms at different gate potentials are presented in the SI.

As the potential of the surface is shifted more cathodic, the conductance histogram shift to higher values and reach a maximum value of $3 \times 10^{-3} \pm 1.4 \times 10^{-3}$ G_o. Thus, the conductance is increased by more than an order of magnitude at potentials more cathodic than the $E_{1/2}$ of the redox reaction. When the pH of the electrolyte was changed from 3 to 8, the increase in the conductance is shifted to more cathodic values. The conductance value reaches a maximum value at ca. -300 mV for pH = 3 and ca. -700 mV for pH = 8. These values are close to the $E_{1/2}$ values obtained at pH = 3 (-305 mV) and pH = 8 (-620 mV) in the CVs and ACVs. Once the potential is shifted back to +300 mV the conductance value was found to restore its original value of $2.5 \times 10^{-4} \pm 1.0 \times 10^{-4}$ G_o which indicates that the switching system is reversible.

As a control experiment, we found that a SAM constructed using a NB bridge (11-NB) that lacked the AQ moiety (Figure 5-inset) displayed no dependence of the conductivity on electrochemical potential over the same potential window that was used for **5AQ5**, at pH= 3 (Figure 5). This finding confirms that the increase in the conductance of **5AQ5** at the $E_{1/2}$ value is due to the redox switch from the AQ to the more conducting H_2AQ moiety.

The conductance of 11-NB is $3.5 \times 10^{-5} \pm 1.2 \times 10^{-5}$ G_o. This value is significantly lower than the conductance of 5AQ5 in the oxidized form ($2.7 \times 10^{-4} \pm 1.1 \times 10^{-4}$ G_o) despite the 5AQ5 being 5 bonds longer than 11-NB. The high conductance of 5AQ5 and 8AQ8 opens up the possibility to design partially conjugated NB bridges that incorporate two or more AQ moieties thus achieving very long molecules that are chemically stable, rigid and can be electrochemically switched to a higher conductance state by reducing the AQ moieties.

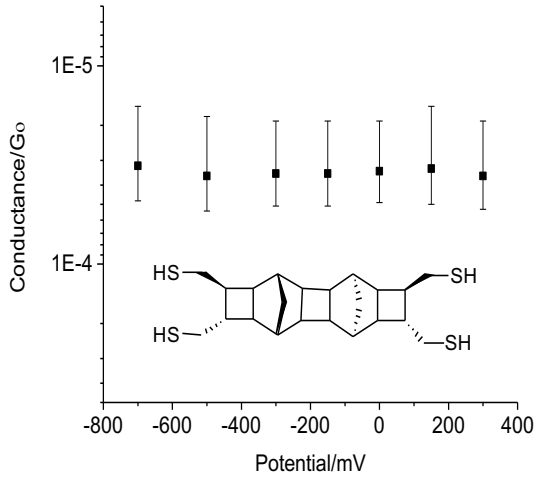

Figure 5. Evolution of the conductance of 11-NB that lacks the AQ moiety, with gate potential at pH=3. Inset is the structure of 11-NB. Typical individual curves along with histograms at different gate potentials are presented in the SI.

In summary, we have demonstrated the successful operation of a single-molecule switch in an AQ-NB system with a conductance on/off ratio of an order of magnitude. This magnitude, which is attributed to destructive QI effects operating in the AQ form,[b] is smaller than that predicted from simple theoretical calculations,[6] but is similar to the experimentally found from bulk conductance studies across SAMs.[7] It is shown that the AQ moiety can be electrochemically switched *in-situ* between the high conducting H_2AQ system and the low conducting AQ system. Further, it is shown that the potential range of the conductance enhancement can be shifted using different pH values. Therefore, such systems could potentially be used as single molecule pH-gated transistors.

Experimental Section

Sample preparation: Gold substrates were prepared by thermally evaporating ca. 100 nm of gold (99.999% Alfa Aesar) on freshly cleaved mica slides (Ted Pella, Inc.) in an ultrahigh-vacuum chamber (~5 × 10^{-8} torr). Prior to each experiment, the substrate was briefly annealed in a hydrogen flame to remove possible contamination and to form an atomically flat surface and then immediately immersed into a 10 μM NB bridge solution in dichloromethane. The substrate was left in the modification solution for 3 hrs after which it was removed, washed thoroughly with DCM and used for the measurements.

Electrochemistry: The redox electrochemistry of SAMs formed on freshly annealed Au (111) substrates of compound **5AQ5** were studied by cyclic voltammetry using a BAS 100B electrochemical analyzer. The counter electrode was a platinum mesh and the reference electrode was a silver wire. The electrolyte used was 0.5 M phosphate buffer using Na_2HPO_4/NaH_2PO_4 for pH=8 and NaH_2PO_4/H_3PO4 for pH =3. The same set up was used to record the ACVs with a Solartron Impedance/Gain-Phase Analyser. The AC amplitude was 15 mV. Data analysis was carried out using the program Z view by Scribner Associates Inc.

Conductance measurements The STM-break junction setup was a modified Pico-STM (Molecular Imaging) using a Nanoscope IIIa controller. The setup and method have been described in details elsewhere.[8] The SAM modified Au (111) substrate was placed in a Teflon STM cell and the surface was covered with toluene. The molecular conductance was measured by repeatedly forming and breaking Au point contacts using an STM gold tip (99.998% Alfa Aesar). The first step was to image the substrate in the regular STM mode. Images showing clear and sharp atomic steps are good indication of a clean substrate and a sharp tip. After surveying the substrate and confirming the tip condition, the tip was fixed at the center of an atomically flat terrace and the STM feedback loop was turned off. Consequently, a Lab View program was used to move the tip into and out of contact with the substrate at a typical rate of 40 nm/s. During the contact process, molecules can bridge between the tip and the molecules on the surface *via* the thiol linkers at the distal end of the molecules. After reaching a preset current value, the tip was pulled back until the current drops to zero. This process was repeated automatically thousands of times. Typically 3000 curves were collected for each experiment. Transient curves that are either noisy or that showed smooth exponential decay due to the absence of a bridging molecule were all rejected when building the histograms. The percentage decay curves that showed clear molecular steps were typically between 20-40% and were all selected for building the histograms.

Keywords: Single molecule conductance· quantum interference· anthraquinone· molecular switches· norbornylogous bridges.

[b] Evidence that the observed electrochemical switching in **5AQ5/5H$_2$AQ5**, is due to QI, rather than to incoherent processes is: (1) For relatively short molecules, such as **5AQ5**, the time-scale for the electrons is expected to be fast compared to the time-scale of vibrations or solvent polarization, so the transport should be coherent. (2) Theoretical work in Ref. 7, confirms the presence of QI in a similar system. (3) The conductance vs. potential plot (Fig. 4) shows a plateau at negative potentials, rather than a drop as would be predicted for an incoherent process, which further confirms that the molecule is either in AQ or H_2AQ form.

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Single molecular switches

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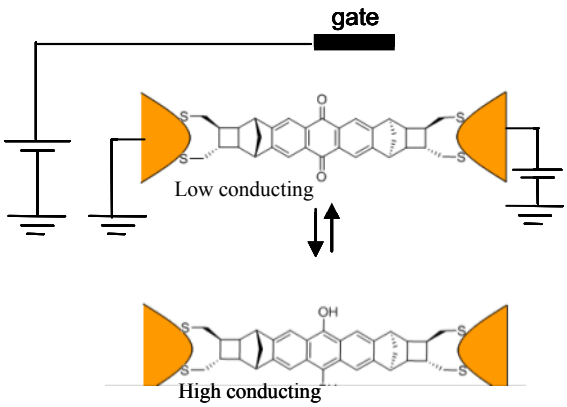

A single-molecular switch based on AQ/H_2AQ redox reaction is demonstrated. It is shown that a single NB-AQ molecule can be switched between a low conducting (NB-AQ) and a high conducting (NB-H_2AQ) using electrochemical gating. The high/low conductance ratio is an order of magnitude. The potential range, upon which the conductance enhancement is observed, can be varied using different pH values of the electrolyte.

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Supporting information

1- STM break junction with electrochemical gating

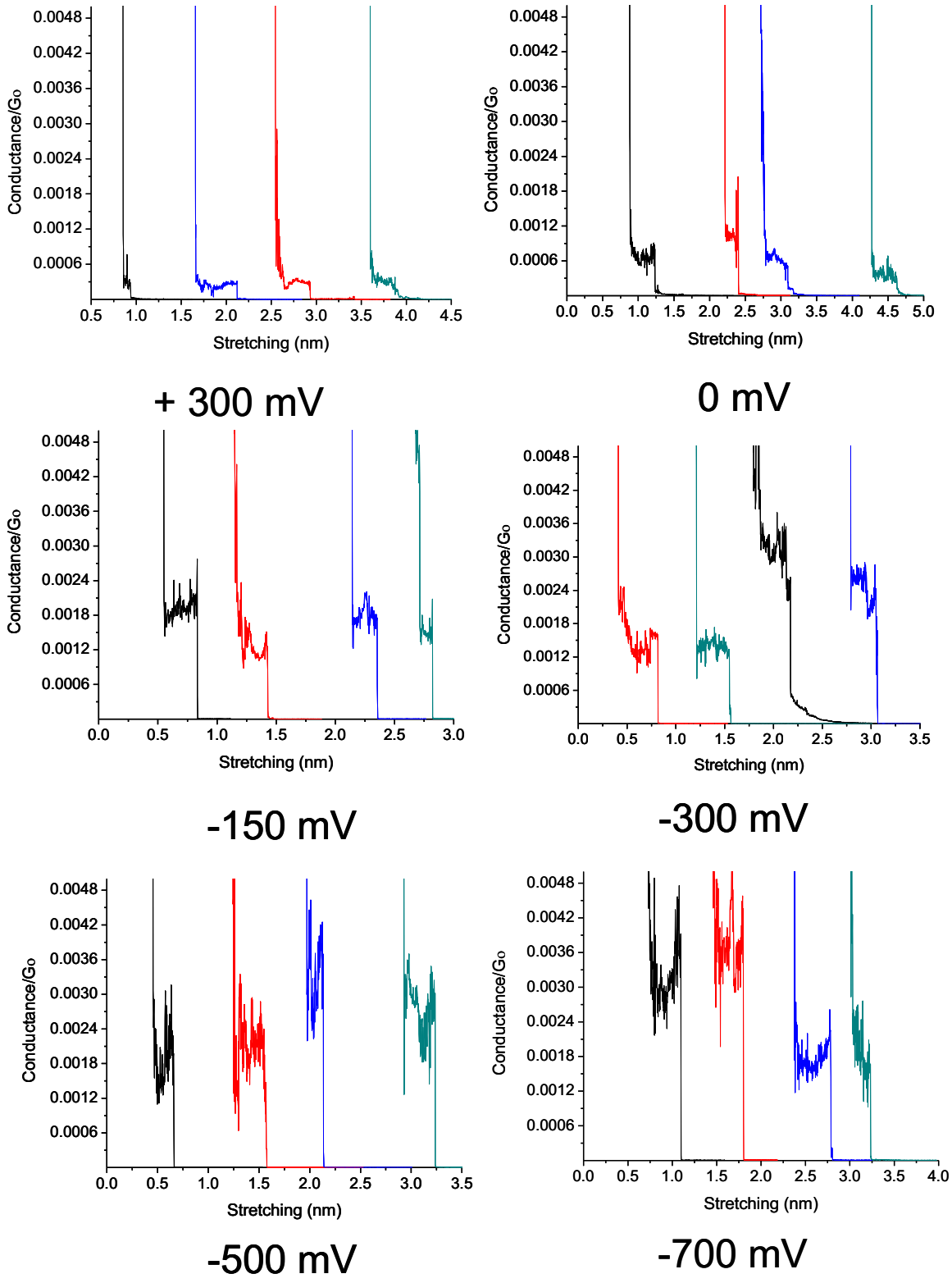


Figure S1. Typical individual transient curves of **5AQ5** at different gate potentials *vs.* Ag at pH = 3.

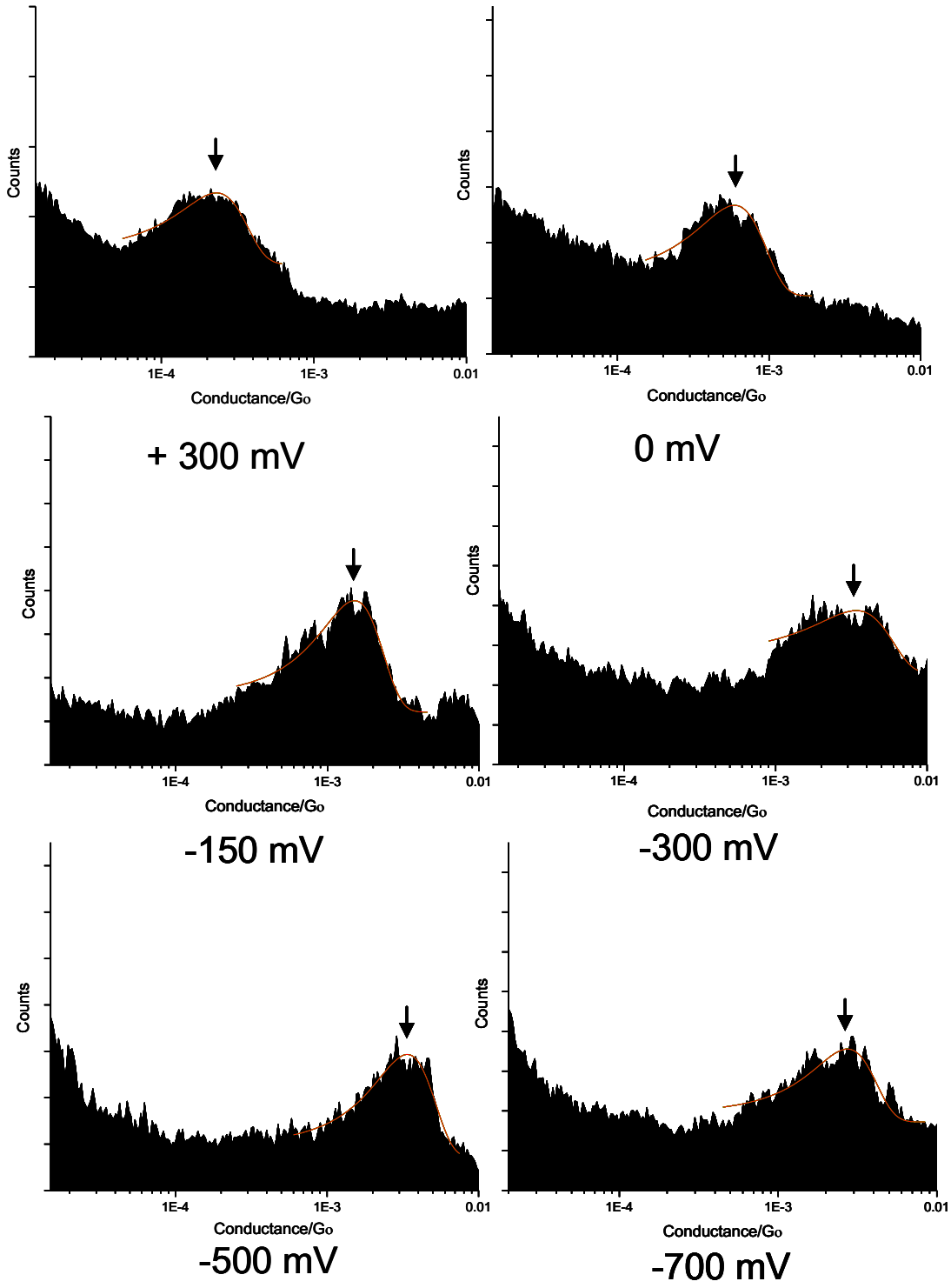


Figure S2. Conductance histograms of **5AQ5** at different gate potentials *vs.* Ag at pH = 3.

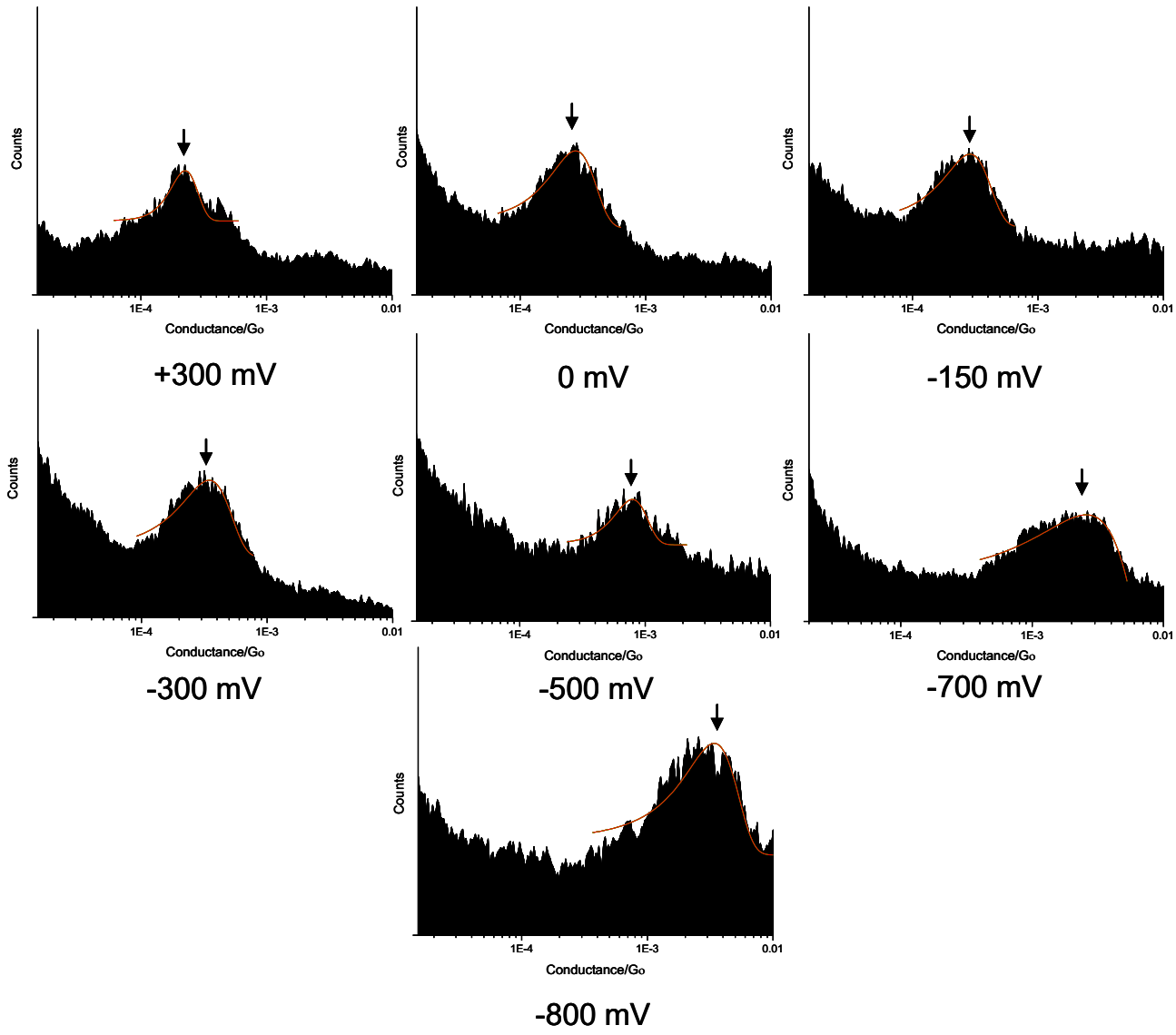
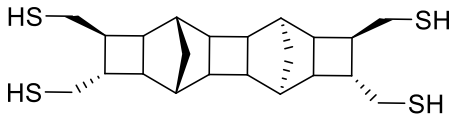


Figure S3. Conductance histograms of **5AQ5** at different gate potentials *vs.* Ag at pH = 8.

11-NB



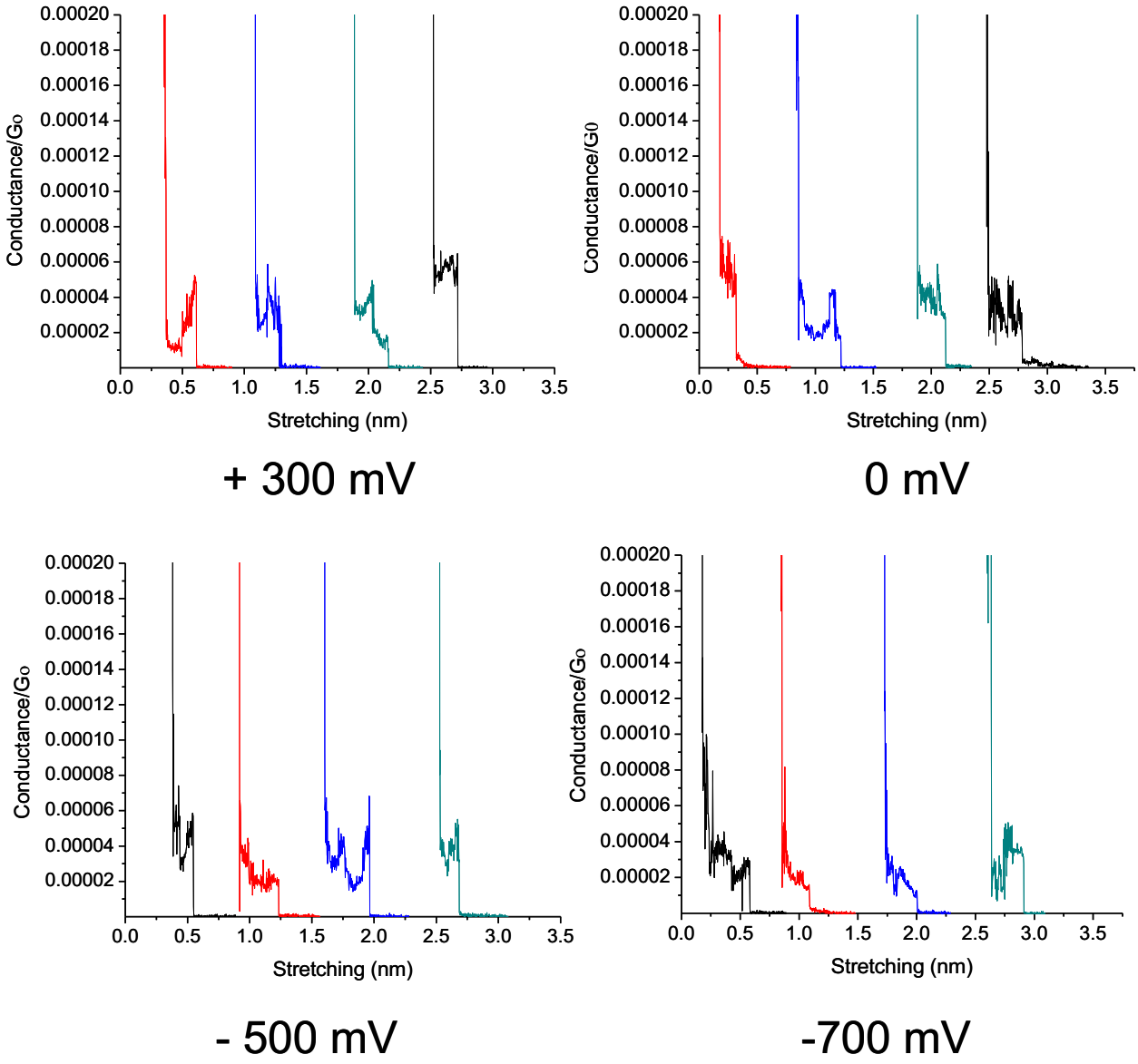


Figure S4. Typical individual transient curves of **11-NB** at different gate potentials *vs.* Ag at pH = 3. **11-NB** was used as a control experiment for the redox gating. The synthesis of **11-NB** is published elsewhere.[1] **11-NB** is a saturated NB bridge molecule. The length of **11-NB is** 14.1 Å, which as in the case of **5AQ5,** is greater than the thickness of the double layer thereby ensuring that the field screening effect due to the proximity of the source and drain electrodes is negligible.

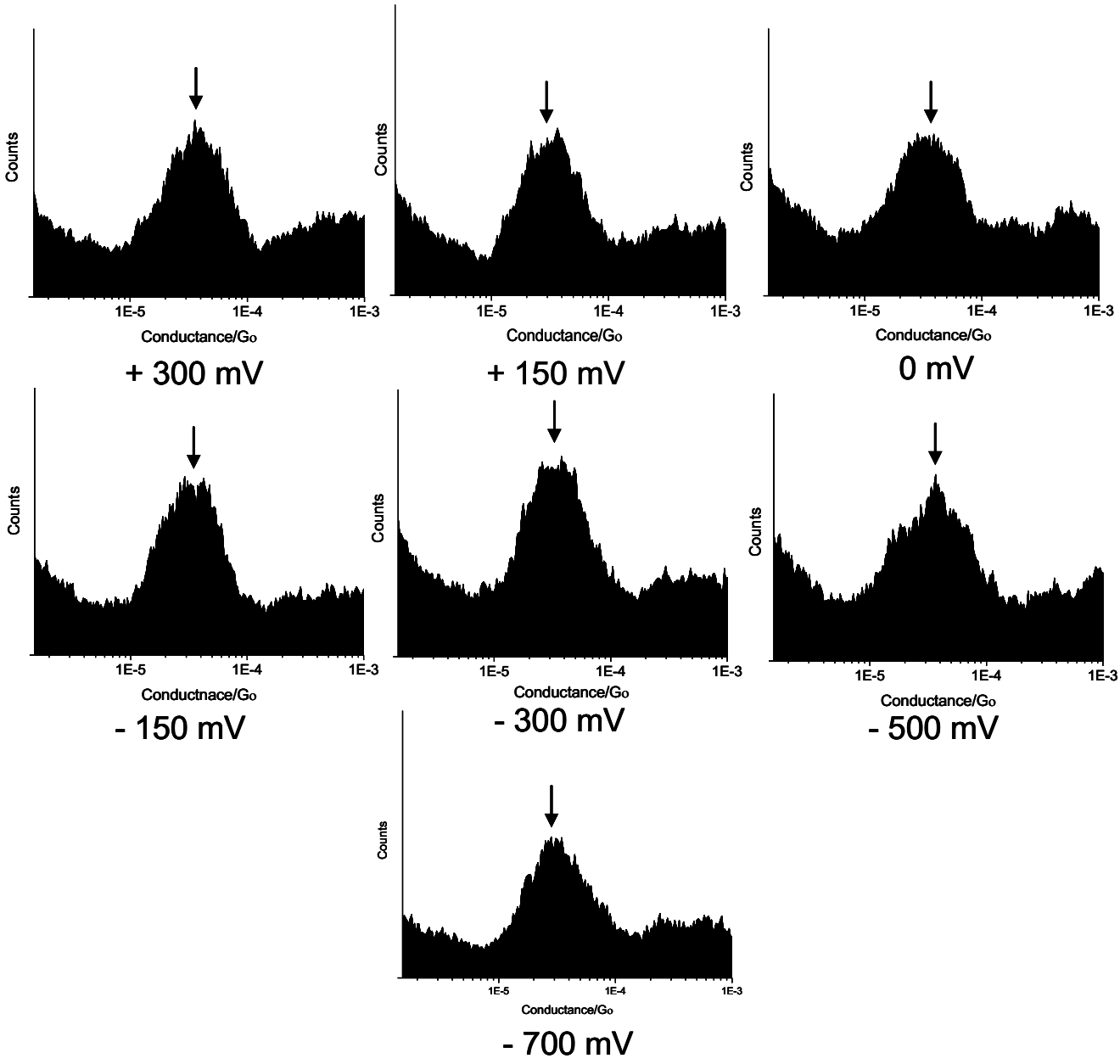


Figure S5. Conductance histograms of **11-NB** at different gate potentials *vs.* Ag at pH = 3.

2- Scanning tunneling microscopy

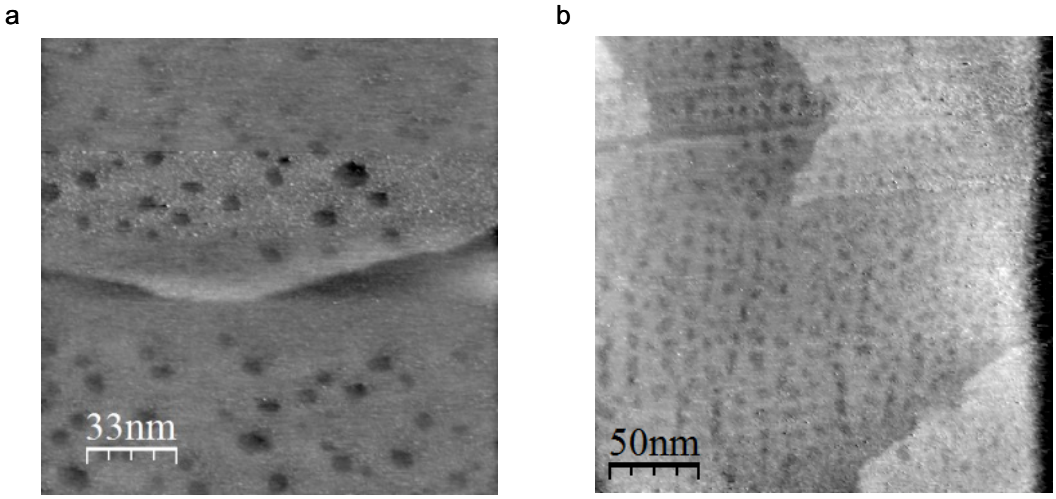


Figure S6. Constant current STM images of SAMs formed of a) **5AQ5**; b) **8AQ8**. Set point current of 0.3 nA and bias voltage of 100 mV. Both SAMs showed a pit-like network of molecules. Such network-structure is commonly observed for thiolated molecules on gold surfaces.[2]

3- X-ray photoelectron spectroscopy

X-ray photoelectron spectroscopy measurements were performed on an ESCALAB 220iXL. Monochromatic Al Kα X-rays (1486.6 eV) incident at 58° to the analyzer lens were used to excite electrons from the sample. Emitted photoelectrons were collected on a hemispherical analyzer with multichannel detector at a takeoff angle of 90° from the plane of the sample surface. The analyzing chamber operated below 10^{-9} mbar and the spot size was approximately 1 mm^2. The resolution of the spectrometer was ~0.6 eV.

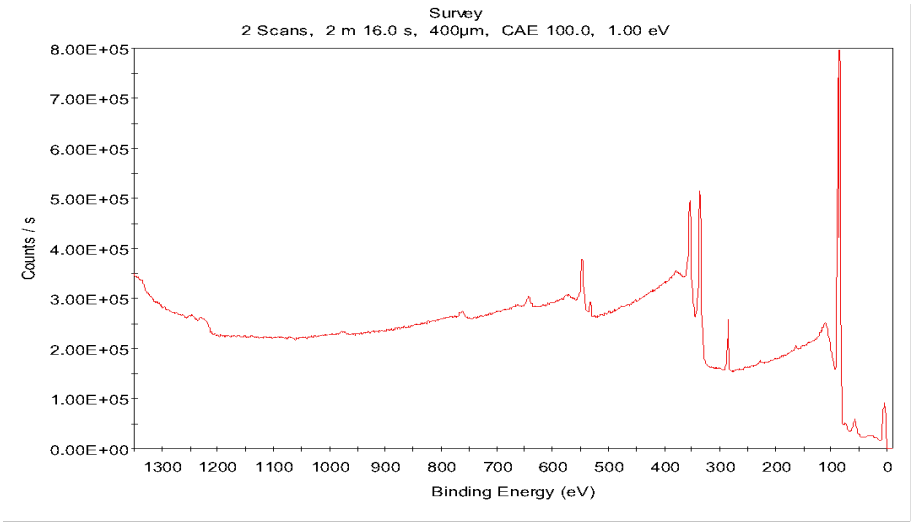


Figure S7. XPS survey scans of a SAM formed of **5AQ5**.

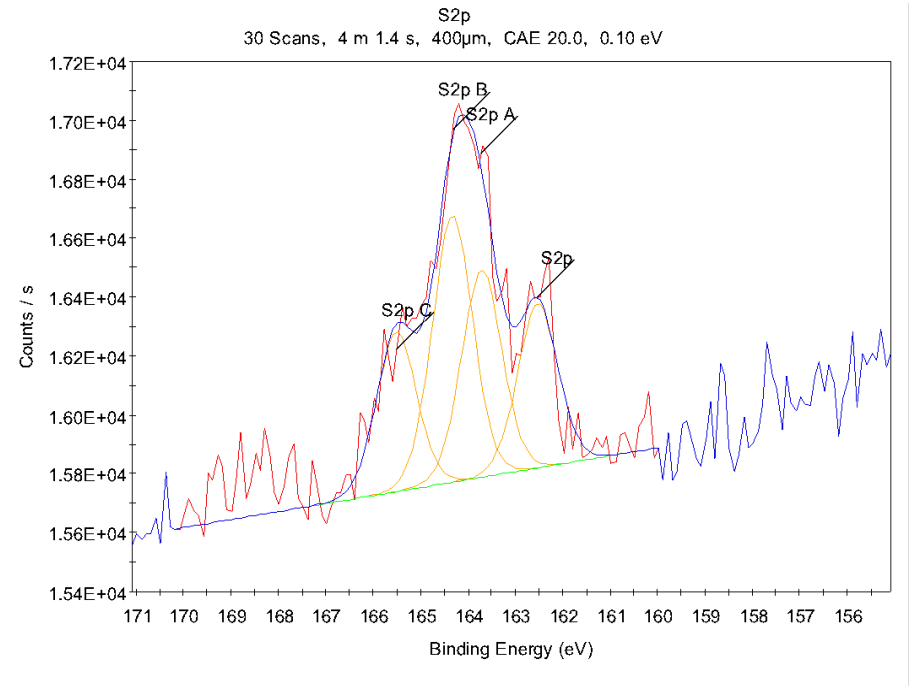


Figure S8. High resolution XPS scans of the S2p region in SAMs formed of **5AQ5**, showing the presence of two different types of thiols: bound-thiol to the gold substrate (162.5, 163.7 eV) and free thiols at the distal end of the monolayer (164.3, 165.5 eV).

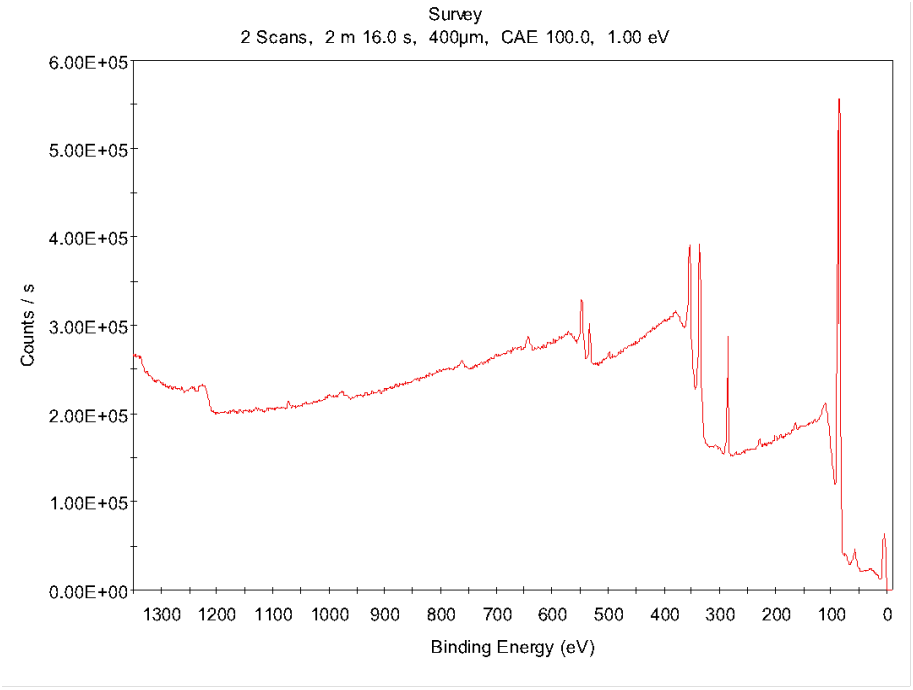


Figure S9. XPS survey scans of a SAM formed of **8AQ8**.

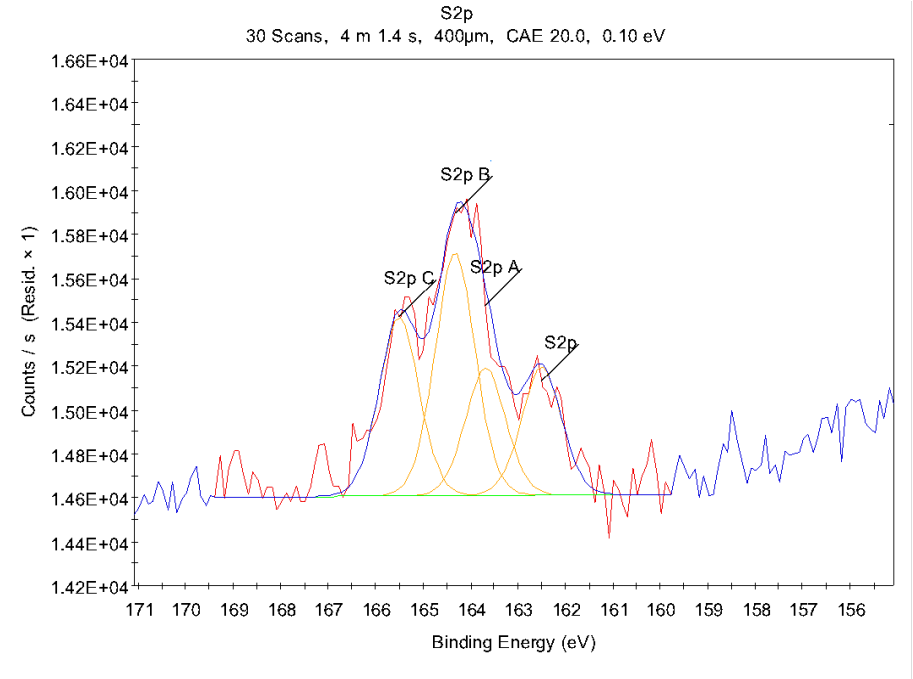


Figure S10. High resolution XPS scans of the S2p region in SAMs formed of **8AQ8**, showing the presence of two different types of thiols: bound thiols to the gold substrate (162.5, 163.6 eV) and free thiols at the distal end of the monolayer (164.3, 165.5 eV). These experiments confirmed that molecules **5AQ5** and **8AQ8** stand straight on the gold surface where the distal free thiols will be easily accessible by the STM gold tip.

4- Cyclic voltammetry

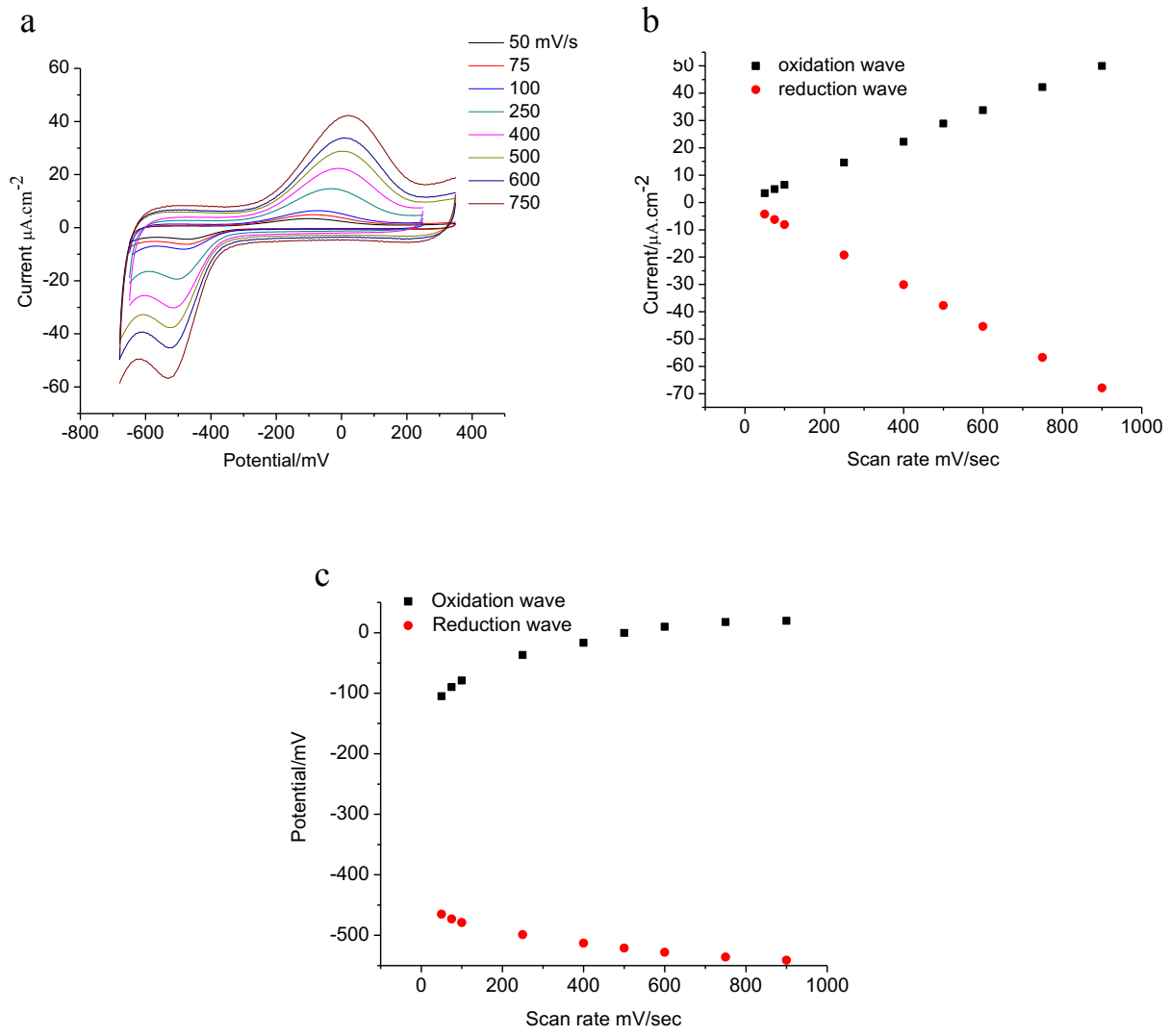


Figure S11. a) Cyclic voltammetry at different scan rate of a SAM formed from 5AQ5 at pH=3. b) Scan rate versus peak current. There exist a linear relationship between the peak currents and the scan rate from 50 mV/s to 900 mV/s which indicates a surface-related redox process. c) Scan rate versus peak potential. The peak separation between the oxidation and the reduction waves increases with increasing scan rate. This is attributed to the slow kinetics of the conversion between the AQ and the H_2AQ states.

5- Synthesis and characterization

5.1 General experimental for the synthesis

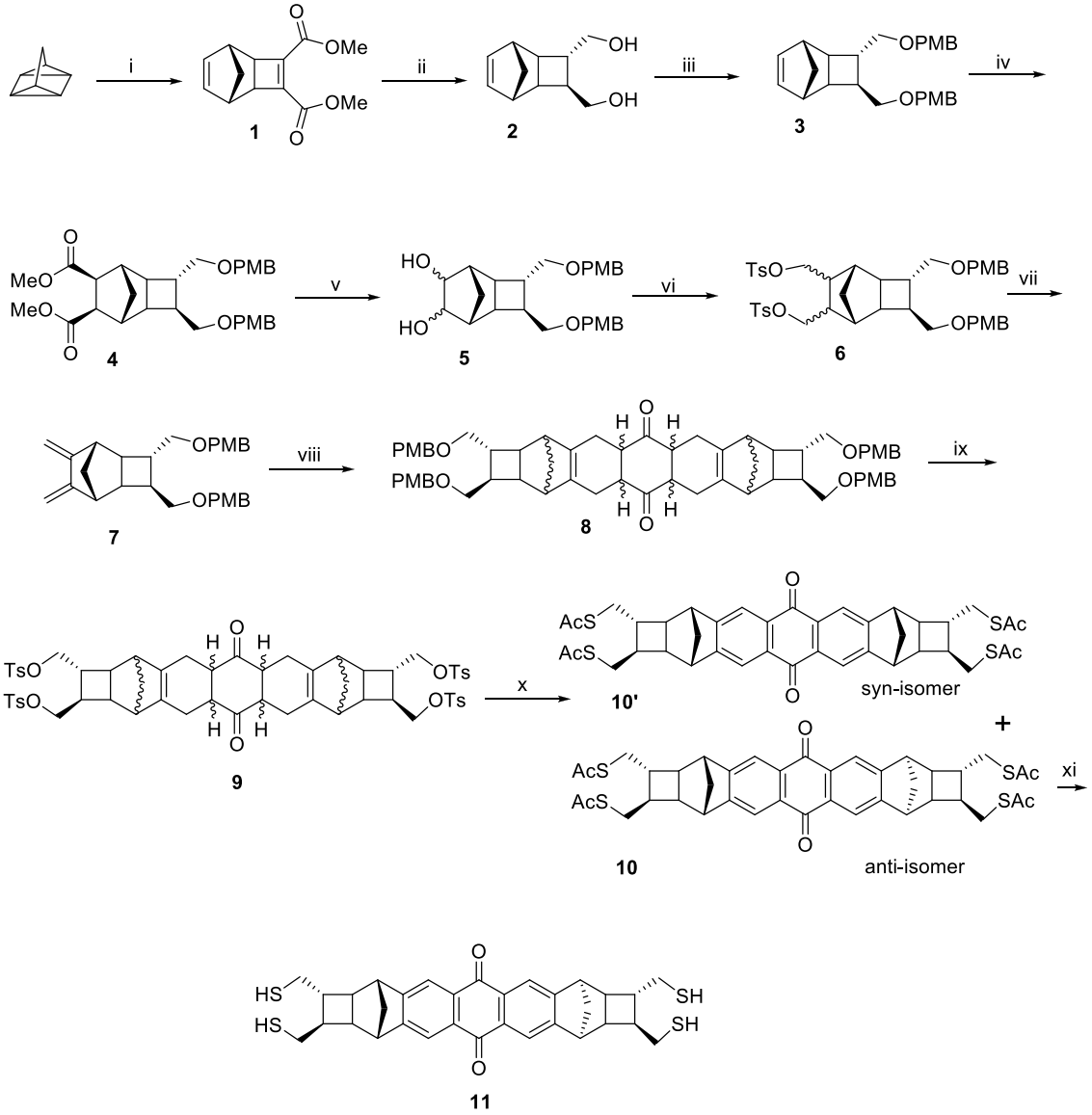
5.2 Synthetic schemes

5.3 Synthetic procedure and characterization of compounds 1-20

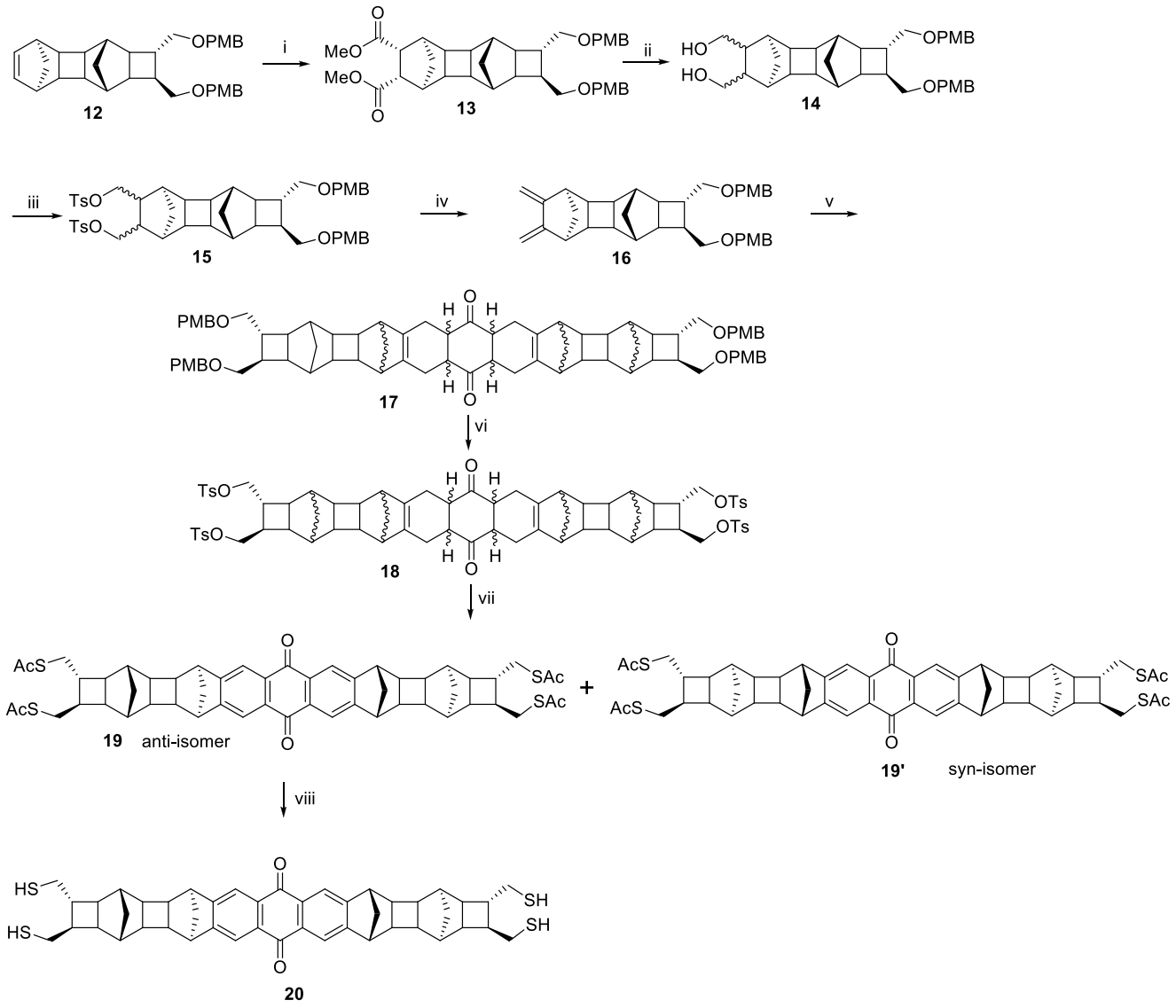
5.1 General experimental for the synthesis

^{1}H NMR spectra were obtained on a Bruker DPX300F (300 MHz) spectrometer. Data is reported as follows: chemical shifts (δ) are measured in parts per million (ppm) relative to TMS and observed coupling constants (*J*) was measured in Hertz (Hz). Multiplicities are reported as singlet (s), broad singlet (bs), doublet (d), triplet (t), broad triplet (bt), quartet (q), doublet of doublets (dd), and multiplet (m). ^{13}C NMR spectra were obtained on a Bruker DPX300F (75.6 MHz) spectrometer. ^{13}C chemical shifts (δ) were reported in parts per million (ppm) and assignments were determined with the aid of one or more of HMBC, HSQC, 90^{o} and 135^{o} DEPT experiments. Cq are quaternary carbon atoms. Flash column chromatography was performed using gravity columns packed with Merck silica gel Type 60 (70-230 mesh). All reagents and solvents involved in the following reactions were purchased from standard suppliers, and used without further purification unless otherwise indicated. Anhydrous THF was freshly distilled from sodium metal and benzophenone under an atmosphere of argon. Anhydrous DCM was freshly distilled from calcium hydride under an atmosphere of argon. Anhydrous benzene was freshly distilled from calcium hydride under an atmosphere of argon and stored over 4 Å molecular sieves. Anhydrous DMF was freshly distilled from calcium hydride under an atmosphere of argon. Anhydrous methanol was freshly distilled from sodium under an atmosphere of argon. DMSO was dried by storing over a 4 Å molecular sieves. Deuterated chloroform was passed through basic alumina before running NMR experiments to remove acidic impurities. Quadricyclane was synthesised according to Dauben and Cargill.[3] The synthesis of compound **12** was reported elsewhere.[4] DMF stands for dimethylformamide. DCM stands for dichloromethane. DDQ stands for 2,3-dichloro-5,6-dicyano-1,4-benzoquinone. DMAD stands for dimethyl acetylenedicarboxylate.

5.2 Synthetic schemes

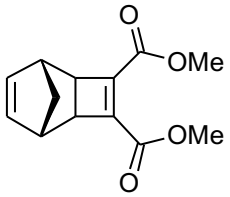


Scheme S1: synthesis of compound 5AQ5.
Reagents: i) DMAD, benzene, reflux, 12 h. ii) $LiAlH_4$, THF, reflux, 72 h. iii) *p*-methoxybenzyl chloride, DMF, monoglyme, r.t. 16 h. iv) $CuCl_2$, sodium acetate, Pd/C, CO, THF, MeOH, r.t.,7 days v) $LiAlH_4$,THF, reflux, 24 h. vi) TsCl, pyridine, -30 °C, 3 days. vii) Potassium *tert*-butoxide, DMF, -10 °C, 12 h. viii) benzoquinone, toluene, 145 °C, 4 d. ix) a) DDQ, H_2O, DCM, 70 °C b) TsCl, pyridine,-10 °C, 24 h. x) KSAc, DMSO, 70 °C, 24 h; b) DDQ, [1,1,2,2 tetrachloroethane], 145 °C, 36 h. xi) HCl, DCM, methanol, reflux, 48 h.

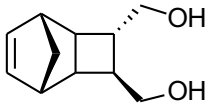


Scheme S2: Synthesis of compound 8AQ8.
Reagents: i) $CuCl_2$, sodium acetate, Pd/C, CO, THF, MeOH, r.t.,7 days. ii) $LiAlH_4$, THF, reflux, 24 h. iii) TsCl, pyridine, -30 °C, 3 days. iv) Potassium *tert*-butoxide, DMF,-10 °C, 12 h. v) benzoquinone, toluene, 145 °C, 4 d. vi) a) DDQ, H_2O, DCM, 70 °C b) TsCl, pyridine,-10 °C, 24 h. vii) a) KSAc, DMSO, 70 °C, 24 h; b) DDQ, [1,1,2,2 tetrachloroethane], 145 °C, 36 h. viii) HCl, DCM, methanol, reflux, 48 h.

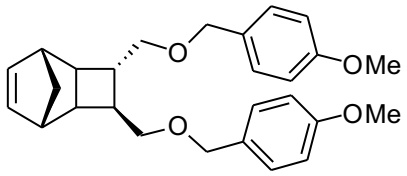
5.3 Synthetic procedure and characterization of compounds 1-20



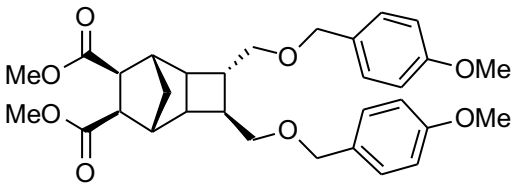
Preparation of 1. Dimethyl acetylenedicarboxylate (DMAD) (42.759 g, 0.301 mol) was added slowly to a solution of quadricyclane (30.778 g, 0.334) in benzene (200 mL). After the addition, the resulting solution was slowly heated to reflux and then allowed to reflux for a further 12 h before it was allowed to cool to room temperature. The resulting solution was then subjected to distillation to give benzene (80 ºC) and DMAD (100 ºC) and upon further distillation under reduced pressure the title compound **1** (69.264 g, 89%) (160-163 ºC at17 mm Hg) was isolated as a pale yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.19 (t, 2H, *J* = 1.9 Hz, CH), 3.80 (s, 6H), 2.71 (s, 2H), 2.60 (s, 2H), 1.38 (q, 2H, *J* = 9.8, 11.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.8 (Cq), 145.1 (Cq), 136.0 (CH), 51.9 (CH_3), 44.2 (CH), 39.6 (CH_2), 38.3 (CH).



Preparation of 2. A solution of Diester **1** (30.812 g, 0.132 mol) in anhydrous tetrahydrofuran (250 mL) was added drop-wise over 1 h to an ice-cold mixture of $LiAlH_4$ (16.691 g, 0.440 mol) in anhydrous tetrahydrofuran (150 mL) under an atmosphere of argon. After the addition the grey mixture was removed from the ice bath and allowed to reflux for 72 h. The resulting grey mixture was then allowed to cool to room temperature before a solution of sodium hydroxide (20 %, 10 mL) and water (10 mL) was added drop-wise over 2 h. The resulting mixture was re-heated and allowed to reflux for 2 h until the grey colour disappeared. The resulting light grey mixture was then filtered hot through a pad of filter aid. The collected solid was then placed into DMF (200 mL) and heated to reflux before the solid was filtered hot through a pad of filter aid extracting any insoluble product. This extracting procedure was repeated in a total of 3 times before the solution was evaporated to dryness under reduced pressure to give a brown coloured solid. The resulting solid was partially dissolved in water (100 mL) before hydrochloric acid (2M, 300 mL) was added resulting in the precipitation of the title compound **2** as a off-white solid (19.379 g, 82%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.97 (ddd, 2H, *J* = 3.0, 5.7, 18.9 Hz, CH), 3.77-3.43 (m, 4H), 2.72 (s, 2H), 2.37-2.21 (m, 1H), 1.97 (t, 1H, *J* = 8.1 Hz), 1.81-1.72 (m, 1H), 1.70-1.64 (m, 2H), 1.29 (d, 1H, *J* = 9.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.6 (CH), 135.0 (CH), 66.8 (CH_2), 60.7 (CH_2), 43.7 (CH), 42.8 (CH_2), 41.2 (CH), 41.0 (CH) , 39.8 (CH) , 36.6 (CH) , 35.8 (CH).

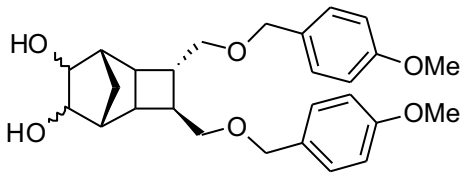


Preparation of 3. Sodium iodide (23.5998 g, 0.1574 mol) was added to a suspension of diol **2** (40.4697 g, 0.2245 mol) in dry DMF (550 mL) and monoglyme (250 mL) under an atmosphere of argon. The resulting suspension was allowed to stir for 30 min before *p*-methoxybenzyl chloride (64 mL, 0.4720 mol) was added. The resulting suspension was allowed to stir for 3 h before the mixture was cooled to 0 ^{o}C in an ice-bath. Sodium hydride (60% suspension in oil, 54.1100 g, 1.3528 mol) was then added in portions over 2 h before the resulting grey mixture was allowed to warm to room temperature over 16 h. After this time, the reaction mixture was quenched with the slow addition of water (500 mL) and the product extracted with diethyl ether (5×200 mL). The combined organic fraction was then washed with brine (3×200 mL), saturated sodium bicarbonate (3×200 mL), water (500 mL), dried with anhydrous magnesium sulphate, filtered and evaporated to dryness under reduced pressure to give a brown liquid. The resulting oil was then subjected to purification by column chromatography (eluent: 100% light petroleum, 25:75 diethyl ether/light petroleum, 50:50 diethyl ether/light petroleum, 75:25 diethyl ether/light petroleum) to give the title compound **3** as a pale yellow liquid (82.040 g, 87%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (d, 4H, *J* = 8.7 Hz), 6.87 (d, 4H, *J* = 8.3 Hz), 5.97 (ddd, 2H, *J* = 3.0, 5.6, 18.1 Hz), 4.44 (s, 2H), 4.43 (s, 2H), 3.80 (s, 6H), 3.58-3.39 (m, 2H), 2.75 (s, 1H), 2.70 (s, 1H), 2.36-2.42 (m, 1H), 1.95 (t, 1H, *J* = 6.8 Hz), 1.75-1.56 (m, 3H), 1.23 (d, 1H, *J* = 9.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4 (Cq), 159.08 (Cq), 159.06 (Cq),136.6 (CH), 135.4 (CH), 135.4 (CH), 130.80 (Cq) 130.78 (Cq), 129.2 (CH), 129.0 (CH), 113.7 (CH), 74.5 (CH_2), 72.6 (CH_2), 68.6 (CH_2), 55.3 (CH_3), 43.9 (CH), 42.4 (CH_2), 41.2 (CH), 38.6 (CH), 37.5 (CH), 36.1 (CH), 34.7 (CH).

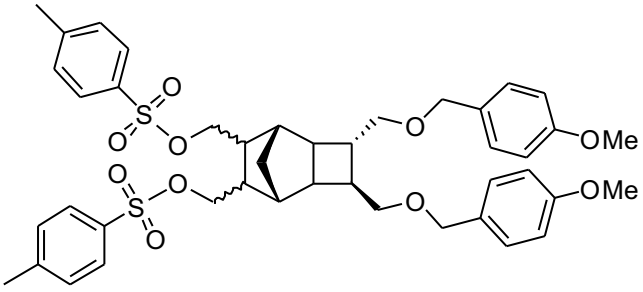


Preparation of 4. Freshly distilled anhydrous tetrahydrofuran (1000 mL) was added to a mixture of anhydrous copper (II) chloride (26.7013 g, 0.1986 mol), anhydrous sodium acetate (16.5959 g, 0.2023 mol) and diether **3** (16.5915 g, 0.0395 mol) under an atmosphere of argon. Anhydrous methanol (1500 mL) was then freshly distilled into the brown coloured mixture resulting in the formation of a dark green coloured mixture. Carbon monoxide was then bubbled through the green mixture for 1 h before 10% palladium on charcoal (1.7175 g) was added and a balloon of carbon monoxide was attached to the reaction flask with the mixture being stirred vigorously for 7 days with more carbon monoxide being introduced as needed. The reaction mixture was then quenched with the addition of water (500 mL) and the resulting dark green mixture was filtered

through filter aid to remove the palladium on charcoal. The collected solid was washed with DCM (100 mL) and the combined filtrate was evaporated down until only the water remained. DCM (1000 mL) was added and the mixture was washed with a solution of 10% ammonia until the blue/green colour no longer remained in the organic layer. The resulting colourless organic layer was washed with saturated sodium bicarbonate (2×500 mL), water (500 mL), dried with anhydrous magnesium sulphate and evaporated to dryness to give a yellow oil. The resulting oil was purified by column chromatography (eluent: 35:65 ethyl acetate/light petroleum) to give the title compound **4** (13.452 g, 63%) as a liquid that solidified on standing. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (d, 4H, *J* = 8.7 Hz), 6.86 (d, 4H, *J* = 8.3 Hz) 4.44 (s, 2H), 4.43 (s, 2H), 3.79 (s, 6H), 3.60 (s, 6H), 3.54-3.395 (m, 2H), 2.52-2.41 (m, 5H), 2.18-2.03 (m, 3H), 1.92-1.85 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.4 (Cq), 173.3 (Cq), 159.1 (Cq), 130.5 (Cq), 130.4 (Cq), 129.3 (CH), 129.2 (CH), 129.1 (CH), 113.7 (CH), 113.6 (CH), 73.5 (CH_2), 72.5 (CH_2), 72.4 (CH_2), 68.2 (CH_2), 55.1 (CH_3), 51.6 (CH_3), 51.5 (CH_3), 49.9 (CH), 49.8 (CH), 49.0 (CH), 42.1 (CH), 39.6 (CH), 39.4 (CH), 38.6 (CH), 37.4 (CH), 32.1 (CH_2).

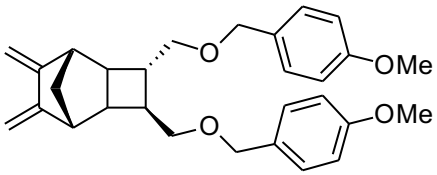


Preparation of 5. A solution of the diester **4** (13.4520 g, 24.97 mmol) in anhydrous tetrahydrofuran (200 mL) was added drop-wise over 30 min into a mixture of lithium aluminium hydride (4.9304 g, 129.90 mmol) in anhydrous tetrahydrofuran (300 mL) under an atmosphere of argon. After the addition the resulting grey coloured mixture was refluxed for 24 h before it was allowed to cool to r.t. and a saturated solution of potassium carbonate (10 mL) was added drop-wise. The resulting mixture was then heated and allowed to reflux for a further 30 min before it was filtered hot through a pad of filter aid. The filtered solid was then washed with boiling tetrahydrofuran/ethyl acetate (1:1, 3×100 mL) solvent mixture to extract the product. The organic fractions were then combined, dried with magnesium sulphate and evaporated to dryness to give the title compound **5** which was not purified any further.



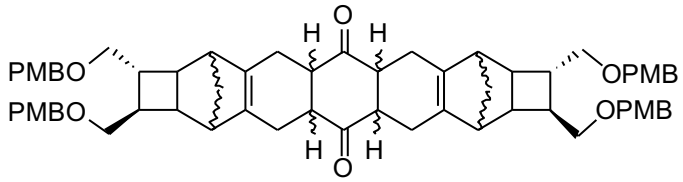
Preparation of 6. Under an atmosphere of argon, tosyl chloride (42.072 g, 0.2207 mol) was added in portions to a cold (−30ºC) solution of dialcohol **5** (17.3251 g, 0.0359 mol) in anhydrous pyridine (600 mL). The resulting dark yellow coloured

mixture was then allowed to stir for 6 h at -30 °C before it was placed into the freezer for a further 3 days with occasional shaking. The resulting dark brown coloured mixture was then placed into a cold bath (-30 °C Ethanol-liquid nitrogen). Cold (-10 °C) DCM (1000 mL) was added and the resulting solution was quenched with the slow addition of cold (-10 °C) hydrochloric acid (2 M, 1000 mL). The mixture was then transferred into a separating funnel and the aqueous layer was removed. The resulting organic layer was washed with cold (-10 °C) hydrochloric acid (2M, 5×500 mL), a cold (-10 °C) saturated solution of sodium bicarbonate (3×500 mL), dried with anhydrous magnesium sulphate and evaporated to dryness to give a dark yellow coloured liquid. The liquid was subjected to column chromatography (eluent: 3:97 diethyl ether/DCM) to give the title compound **6** (14.6234 g, 51%) as a pale yellow oil that solidified on standing. ^{1}H NMR (300 MHz, $CDCl_3$) 7.77 dd (1.7, 8.4 Hz, 4H), 7.33 dd (1.7 Hz, 8.4 Hz), 7.21 (dt, 4H, *J* = 2.4, 6.9 Hz, CH), 6.87 (dt, 4H, *J* = 2.1, 8.7 Hz, CH), 4.39 (s, 2H), 4.35 (s, 2H), 3.91-3.88 (m, 2H), 3.82-3.76 (m, 2H), 3.70 (s, 6H), 2.44 (s, 6H), 2.08-2.05 (m, 2H), 1.97-1.95 (m, 2H), 1.84-1.80 (m, 2H), 1.73 (s, 2H), 1.61 (d, *J* = 10 Hz, 1 H), 1.22 (d, J= 10 Hz, 1 H).^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1 (Cq), 159.0 (Cq), 144.9 (Cq), 144.8 (Cq), 132.5 (Cq), 132.4 (Cq), 130.4 (Cq), 130.3 (Cq), 129.9 (CH), 129.1 (CH), 129.0 (CH), 127.7 (CH), 113.62 (CH), 113.59 (CH), 73.6 (CH_2), 72.5 (CH_2), 72.4 (CH_2), 69.4 (CH_2), 69.3 (CH_2), 68.1 (CH_2), 55.1 (CH_3), 55.0 (CH_3), 43.5 (CH), 42.5 (CH), 42.2 (CH), 41.6 (CH), 39.9 (CH), 38.9 (CH), 38.7 (CH), 37.3 (CH), 30.0 (CH_2), 21.6 (CH_3).

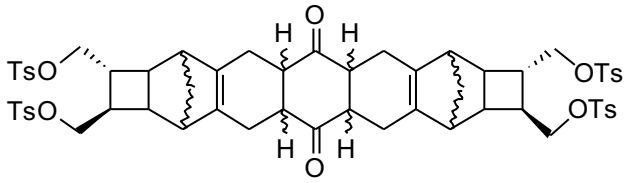


Preparation of 7. Under an atmosphere of argon, anhydrous dimethyl formamide (240 mL) was freshly distilled into a flask containing ditosylate **6** (3.8575 g, 4.877 mmol). The resulting solution was then cooled in an ice/salt (-10 °C) bath and potassium *tert*-butoxide (2.7876 g, 24.842 mmol) was added in portions over 30 min. The resulting red/brown coloured solution was then allowed to stir for 12 h before it was quenched with the slow addition of cold (-10 °C) hydrochloric acid (2M, 100 mL). The resulting cream coloured suspension was then transferred into a separating funnel, water (900 mL) was added and the product was extracted with DCM (5×200 mL). The combined organic fractions were then washed with hydrochloric acid (2M, 500 mL), saturated sodium bicarbonate (500 mL), dried with magnesium sulphate and evaporated to dryness to give a yellow oil. The oil was subjected to column chromatography (eluent: 5:95 diethyl ether/light petroleum, 10:90 diethyl ether/light petroleum, 50:50 diethyl ether/light petroleum) to furnish the title compound **7** (1.4148 g, 65 %) as a pale yellow coloured oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (dt, 4H, *J* = 2.4, 6.9 Hz), 6.87 (dt, 4H, *J* = 2.1, 8.7 Hz), 5.10 (s, 1H), 5.06 (s, 1H), 4.77 (s, 1H), 4.74 (s, 1H), 4.42 (d, 4H, *J* = 1.2 Hz), 3.80 (s, 6H), 3.57-3.39 (m, 4H), 2.73 (s, 1H), 2.67 (s, 1H), 2.52-2.46 (m, 1H), 2.27 (t, 1H, *J* = 7.2 Hz), 2.12 (t, 1H, *J* = 5.1 Hz), 1.93-1.89 (m, 2H), 1.41 (d, 1H, *J* = 10.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1 (Cq), 151.3 (Cq), 150.6 (C),130.7 (Cq), 130.6 (Cq), 129.3 (CH), 129.2 (CH) 129.1 (CH), 113.72 (CH), 113.70

(CH), 100.7 (CH_2), 100.0 (CH_2), 74.2 (CH_2), 72.6 (CH_2), 68.5 (CH_2), 55.2 (CH_3), 47.5 (CH), 44.7 (CH), 41.9 (CH), 39.2 (CH), 39.1 (CH), 37.9 (CH), 34.7 (CH_2). HRMS (ESI) m/z calculated for **7** $[M+Na]^+$ 469.2335, found 469.2346.

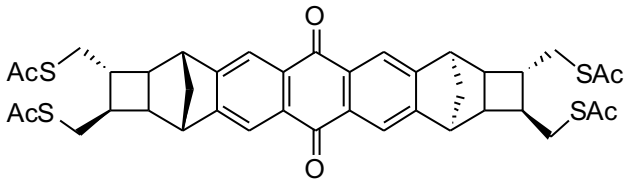


Preparation of 8. To a solid portion of **7** (1.0556 g, 2.363 mmol) was added a solid portion of benzoquinone (127.71 mg, 1.1815 mmol) in a pressure tube. The mixture was then dissolved in dry toluene (4 mL). The solution mixture was then degassed by bubbling argon for 20 min before the pressure tube was sealed and heated at 145 °C for 4 days. The solvent was then evaporated under reduced pressure to give a pale yellow solid. The solid was subjected to column chromatography (eluent: 2:98 ethylacetate/DCM) to furnish the title compound **8** as pale yellow colour (1.20 g, 93%). The title compound contains a mixture of isomers which were not separated on the column at this stage. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (dd, 8H, *J* = 2.1, 8.7 Hz), 6.86 (dd, 8H, *J* = 2.1, 8.7 Hz), 4.42 (s, 4H), 4.41 (s, 4H), 3.81 (s, 12H), 3.43 (m, 8H), 2.90-2.68 (m, 3H), 2.60-2.40 (m, 8H), 2.36-2.19 (m, 4H), 2.16-1.16 (m, 7H), 1.31-1.15 (m, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1 (Cq), 131.9 (Cq), 130.8 (Cq), 129.7 (CH), 114.2 (CH), 113.5 (CH), 74.2 (CH_2), 72.7(CH_2), 68.6 (CH_2), 55.2 (CH_3), 47.5 (CH), 47.2 (CH), 46.8(CH), 44.8 (CH), 44.5 (CH), 44.2 (CH), 40.9 (CH_2), 41.2 (CH_2), 38.7 (CH), 38.3 (CH), 35.6 (CH), 35.3 (CH), 33.6 (CH), 33.2 (CH_2). HRMS (ESI) m/z calculated for **8** $[M+H]^+$ 1001.5204, found 1001.5219.



Preparation of 9. To a solution of **8** (610 mg, 0.609 mmol) dissolved in DCM (40 mL) and water (5 mL) in a pressure tube was added a solid portion of DDQ (650 mg, 2.860 mmol). The resulting brown mixture was heated for 3 h at 70° C after which it was cooled to room temperature. 1,4 cyclohexadiene (1 mL) was then added and the reaction mixture was left stirring for 30 min at room temperature. The solvents were then removed under reduced pressure furnishing a dark brown solid which was not purified any further. The dark brown solid was then redissolved in anhydrous pyridine (30 mL) and the mixture was cooled in an acetone-ice bath to -10 °C. Tosyl chloride (1.40 g, 7.343 mmol) was then added in small portions under argon. The resulting mixture was left at -10 °C for 24 h after which ice cold DCM was added and the mixture was transferred to a separatory funnel. The organic phase was washed with 2 M HCl (5×100 mL) and then washed with a saturated solution of $NaHCO_3$, water (2×100 mL) and dried with sodium sulphate. The solvent was then evaporated under reduced pressure to furnish an orange coloured solid. The solid was subjected to column chromatography eluent (100 % DCM to elute the excess tosyl chloride and the *p*-methoxy benzylaldehyde and then (10:90 ethyl acetate/DCM to furnish the title compound **9** as a yellow solid. (303 mg, overall yield: 44%). Note that several fractions which correspond to the isomers of the same title

compound (very close Rf values) could be separated on the column at this stage. However, these fractions were combined and taken to the next step and the separation of isomers was left to a later stage. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, J = 8.1 Hz, 8H), 7.34 (d, J = 8.1 Hz, 8H), 4.10-3.90 (m, 4H), 3.88-3.79 (m, 4H), 3.30-3.15 (m, 2H), 2.75-2.55 (m, 3H), 2.53-2.49 (m, 3H), 2.46 (s, 12H), 2.30-1.80 (m , 16H), 1.29 (m, 2H).^{13}C NMR (75 MHz, $CDCl_3$) δ 145.2 (Cq), 133.3 (Cq), 130.2 (CH), 128.0 (CH), 72.8 (CH_2), 68.5 (CH_2), 46.1 (CH_2), 42.7 (CH), 41.5 (CH), 38.0 (CH), 36.2 (CH), 30.1 (CH_2), 21.8 (CH_3). HRMS (ESI) m/z calculated for **9** $[M+Na]^+$ 1159.3077, found 1159.3040.



Preparation of 10. To a solution of **9** (298 mg, 0.255 mmol) in anhydrous DMSO (20 mL) was added a solid portion of potassium thioacetate (291 mg, 2.55 mmol) under argon. The solution mixture was heated at 70 °C for 24 h after which it was cooled to room temperature. The solution mixture was then transferred to a separatory funnel where DCM (100 mL) and water (100 mL) were added. The organic phase was further washed with water (5×100 mL), dried with sodium sulphate and the solvent was evaporated under reduced pressure to furnish a pale yellow solid. The solid was not purified any further and was dissolved in anhydrous 1,1,2,2 tetrachloroethane (15 mL) in a pressure tube. A solid portion of DDQ (276 mg, 1.21 mmol) was then added under argon and the solution mixture was heated at 145 °C for 36 h after which was cooled to room temperature. 1,4 cyclohexadiene (1 mL) was then added and the mixture was left stirring for 30 min at room temperature. The solvent was then evaporated to furnish a dark brown solid. The solid was subjected to column chromatography eluent (100% DCM) and then (5:95 ethyl acetate-DCM solvent mixture) to give the title compound (63.4 mg, overall yield: 34 %). The product was further subjected to column chromatography in order to separate the *syn* and the *anti* isomers eluent (2:98 ethyl acetate-DCM solvent mixture to furnish two fractions: a higher Rf *syn* isomer **10'** (65%, 41.2 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (s, 2H), 8.00 (s, 2H), 3.43 (s, 2H), 3.35 (s, 2H), 3.30-3.10 (m, 4H), 3.00-2.72 (m, 4H), 2.38 (s, 6H), 2.36 (s, 6H), 2.35-2.00 (m, 6 H), 1.95-1.75 (m, 6H).^{13}C NMR (75 MHz, $CDCl_3$) δ 195.6 (Cq), 195.5 (Cq), 183.7 (Cq), 153.9 (Cq), 153.2 (Cq), 132.5 (Cq), 119.3 (CH), 118.9 (CH), 45.8 (CH), 43.1 (CH_2), 43.0 (CH), 41.8 (CH), 39.7 (CH), 38.5 (CH), 38.0 (CH), 34.6 (CH_2), 30.7 (CH_3), 27.4 (CH_2). HRMS (ESI) m/z calculated for the *syn* isomer **10'** $[M+Na]^+$ 767.1605 , found 767.1590 and the title lower Rf *anti* isomer **10** (35 %, 22.2 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (s, 2H), 7.99 (s, 2H), 3.43 (s, 2H), 3.36 (s, 2H), 3.30-3.10 (m, 4H), 3.01-2.70 (m, 4H), 2.39 (s, 6H), 2.36 (s, 6H), 2.35-2.00 (m, 6 H), 1.95-1.75 (m, 6H).^{13}C NMR (75 MHz, $CDCl_3$) δ 195.8 (Cq), 195.6 (Cq), 183.8 (Cq), 154.1 (Cq), 153.3 (Cq), 132.6 (Cq), 119.5 (CH), 119.0 (CH), 46.1 (CH), 43.4 (CH_2), 43.2 (CH), 42.0 (CH), 40.0 (CH), 38.7 (CH), 38.2 (CH), 34.8 (CH_2), 30.9 (CH_3), 27.6 (CH_2). HRMS (ESI) m/z calculated for **10** $[M+H]^+$ 745.1786, found 745.1767.

The preferred *syn* adduct formation has been observed in Diels-Alder reactions similar to those described here.[5, 6] The identification of the isomers were ascertained by an X-ray crystal structure of the *anti* (non-preferred adduct) tetra thioacetate precursor of compound **19** that followed similar procedures to those described here. (see preparation of compound **19**).

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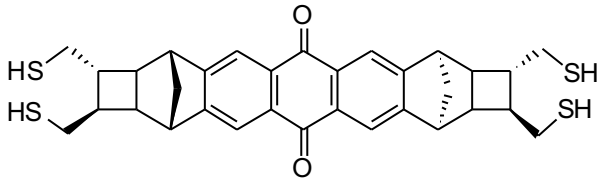
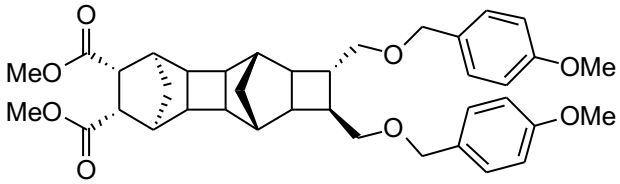
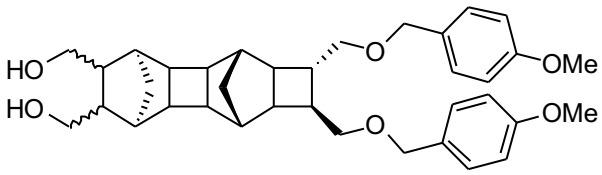


Preparation of 11. To a solution of **10** (22 mg, 0.038 mmol) in degassed DCM (10 mL) and degassed methanol (40 mL) was added concentrated HCl (200 μL). The mixture was further degassed by bubbling argon from 10 min. The reaction mixture was then brought to reflux under argon for 48 h after which it was allowed to cool to room temperature. Water (100 mL) was then added and the two layers separated. The organic layer was further washed with saturated sodium bicarbonate (2×100 mL), water (2×100 mL), dried by sodium sulphate and evaporated to dryness furnishing the title compound **11** as a yellow solid (16.1 mg, 94 %).^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (s, 2H), 8.02 (s, 2H), 3.52 (s, 2H), 3.41 (s, 2H) 2.90-2.50 (m, 8H), 2.40-2.05 (m, 6H), 1.97-1.72 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 183.7 (Cq), 154.0 (CH), 153.3 (CH), Cq (132.7), Cq (119.5), Cq (118.9), 46.0 (CH), 44.0 (CH), 43.3 (CH_2), 42.8 (CH), 42.5 (CH), 41.7 (CH), 37.8 (CH), 30.6 (CH_2), 23.3 (CH_2).

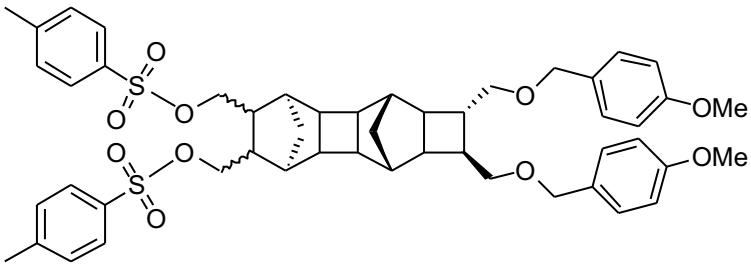


Preparation of 13. Under an atmosphere of argon, freshly distilled anhydrous tetrahydrofuran (500 mL) was added to a mixture of anhydrous copper (II) chloride (11.94 g, 88.82 mmol), anhydrous sodium acetate (7.13g, 86.94 mmol) and diether **12**[4] (8.67 g, 16.91 mmol) before anhydrous methanol (800 mL) was freshly distilled into the brown coloured mixture resulting in the formation of a dark green coloured mixture. Carbon monoxide was then bubbled through the green mixture for 1 h before 10 % palladium on charcoal (0.896 g) was added and a balloon of carbon monoxide attached to the reaction flask with the mixture being stirred vigorously for 7 days with more carbon monoxide being introduced as needed. The reaction mixture was then quenched with the addition of water (500 mL) and the resulting dark green mixture was filtered through filter aid to remove the palladium on charcoal. The collected solid was washed with DCM (100 mL) and the combined filtrate was evaporated down until only the water remained. DCM (800 mL) was added and the mixture was washed with a solution of 10 % ammonia until the blue/green colour no longer remained in the organic layer. The resulting colourless organic layer was washed with saturated sodium bicarbonate (2×500 mL), water (500 mL), dried with anhydrous magnesium sulphate and evaporated to dryness to give a yellow liquid. The resulting oil was purified by column chromatography (eluent: 35:65 ethyl

acetate/light petroleum) to give the title compound **13** (7.91 g, 74 %) as a liquid that solidified on standing.^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.26 (d, J = 8.4 Hz, 4H), 6.85 (d, J = 8.4 Hz, 4H), 4.39 (s, 4H), 3.80 (s, 6H), 3.60 (s, 6H), 3.59-3.30 (m, 4H), 2.49 (s, 2H), 2.48 (s, 2H), 2.43 (m, 1H), 2.04-1.70 (m, 9H), 1.64 (s, 2H), 1.41 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.5 (Cq), 173.6 (Cq), 158.9 (Cq), 130.6 (Cq), 130.5 (Cq), 129.1 (CH), 128.9 (CH), 112.6 (CH), 74.2 (CH_2), 72.4 (CH_2), 68.7 (CH_2), 55.1 (CH_3), 51.6 (CH_3), 45.4 (CH), 44.7 (CH), 44.6 (CH), 44.3 (CH), 43.8 (CH), 41.2 (CH), 41.3 (CH), 39.5 (CH), 38.6 (CH), 37.9 (CH), 36.6 (CH), 36.6 (CH), 29.8 (CH_2), 25.8 (CH_2).

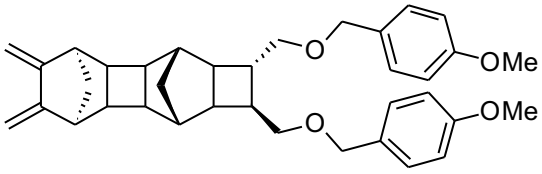


Preparation of 14. A solution of the diester **13** (7.913g, 12.546 mmol) in anhydrous tetrahydrofuran (250 mL) was added drop-wise over 30 min to a mixture of lithium aluminium hydride (3.497g, 92.099 mmol) in anhydrous tetrahydrofuran (100 mL) under an atmosphere of argon. After the addition the resulting grey coloured mixture was then refluxed for 24 h before it was allowed to cool to r.t. and a saturated solution of potassium carbonate (10 mL) was added drop-wise. The resulting mixture was then heated and allowed to reflux for a further 30 min before it was filtered hot through a pad of filter aid. The filtered solid was then washed with boiling tetrahydrofuran (3×100 mL) to extract the product. The organic fractions were then combined, dried with magnesium sulphate, filtered and evaporated to dryness to give the title compound **14** which was not purified any further.

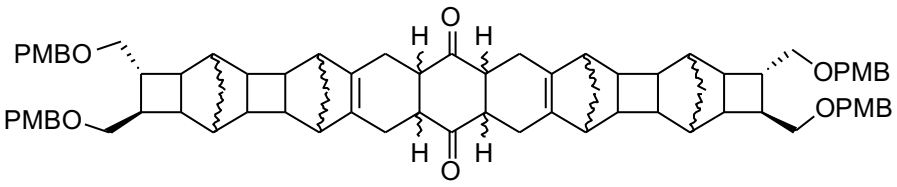


Preparation of 15. A solution of tetraalcohol **14** (7.813 g, 12.497 mmol) in anhydrous pyridine (200 mL) was cooled in a cold bath (−30ºC, ethanol/liquid nitrogen) under an atmosphere of argon before tosyl chloride (13.38 g, 70.42 mmol) was added in portions over 1 h. The resulting mixture was then stirred vigorously for a further 5 h before it was placed into the freezer for 3 days. The reaction mixture was returned to a cold bath (−30 ºC, ethanol/liquid nitrogen) before cold (-10 ºC) DCM (200 mL) and cold (−10 ºC) hydrochloric acid (2 M, 200 mL) were added and stirred for a further 10 min. The organic layer was separated, washed with cold (−10 ºC) hydrochloric acid (2 M, 5×250 mL), saturated sodium bicarbonate (500 mL), dried with anhydrous magnesium sulphate, filtered and evaporated to dryness under reduced pressure furnishing a cream coloured solid. The resulting solid was then subjected to purification by flash chromatography (eluent: 100% dichlormethane) furnishing the

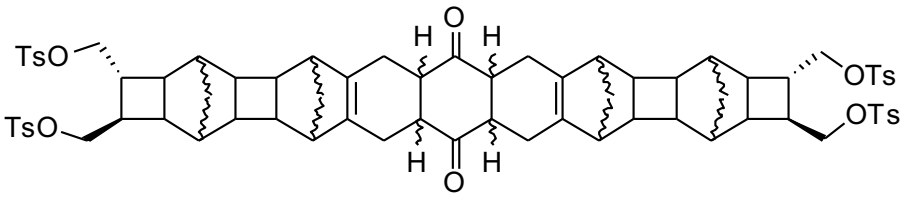
title compound **15** (8.120 g, 66 %) as a white coloured solid. ^{1}H NMR (300 MHz, $CDCl_3$) 7.78 (d, *J*= 8.4 Hz, 4H), 7.35 (d, *J* = 8.4 Hz, 4H), 7.22 (dt, 4H, *J* = 2.4, 6.9 Hz, CH), 6.88 (dt, 4H, *J* = 2.1, 8.7 Hz), 4.40 (s, 2H), 4.37 (s, 2H), 3.92-3.87 (m, 2H), 3.83-3.76 (m, 2H), 3.70 (s, 6H), 2.44 (s, 6H), 2.08-2.05 (m, 2H), 1.97-1.92 (m, 8H), 1.84-1.79 (m, 4H), 1.73 (s, 2H), 1.61 (d, *J* = 10 Hz, 1 H), 1.22 (d, *J* = 10 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1 (Cq), 144.8 (Cq), 144.7 (Cq), 132.3 (Cq), 132.2 (Cq), 130.7 (Cq), 130.4 (Cq), 129.8 (CH), 129.3 (CH), 129.2 (CH), 127.5 (CH), 113.7 (CH), 113.6 (CH), 73.8 (CH_2), 72.6 (CH_2), 72.6 (CH_2), 69.7 (CH_2), 69.5 (CH_2), 68.1 (CH_2), 55.1 (CH_3), 55.0 (CH_3), 43.4 (CH), 42.4 (CH), 42.2 (CH), 41.9 (CH), 41.6 (CH), 39.8 (CH), 39.3 (CH) 38.9 (CH), 38.6 (CH), 38.1 (CH), 37.1 (CH), 30.0 (CH_2), 29.8 (CH_2), 21.3 (CH_3).



Preparation of 16. Under an atmosphere of argon, anhydrous dimethyl formamide (100 mL) was freshly distilled into a flask containing ditosylate **15** (4.002g, 4.532 mmol) and the resulting solution was then cooled in an ice/salt (−10 °C) bath. Potassium *tert*-butoxide (2.664 g, 23.788 mmol) was then added in portions over 30 min to the solution before it was allowed to stir for a further 12 h. The red/brown solution was then quenched with the slow addition of cold (-10 °C) hydrochloric acid (2 M, 100 mL) resulting in the formation of a cream coloured suspension. The mixture was transferred into a separating funnel, water (750 mL) was added and the product extracted with DCM (5×200 mL). The combined organic fractions were then washed with hydrochloric acid (2M, 500 mL), saturated sodium bicarbonate (500 mL), dried with magnesium sulphate, filtered and evaporated to dryness to give a yellow coloured liquid. The resulting oil was subjected to purification by gradient column chromatography (eluent: 5:95 diethyl ether/light petroleum, 10:90 diethyl ether/light petroleum, 50:50 diethyl ether/light petroleum) to furnish the title compound **16** (2.153 g, 88 %) as a pale yellow coloured solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.23 (dt, 4H, *J* = 1.5 Hz, 8.4 Hz), 6.86 (d, 4H, *J* = 8.4), 5.08 (s, 2H), 4.74 (s, 2H), 4.40 (s, 4H), 3.80 (s, 6H), 3.59-3.35 (m, 4H), 2.56 (s, 2H), 2.44 (m, 1H), 2.07 (d, *J* = 9.9 Hz, 1 H), 1.76-1.73 (m, 2H), 1.50-1.43 (m, 2H), 1.37 (d, *J* = 9.9 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ Cq (159.1), Cq (159.0), Cq (151.0), Cq (130.8), Cq (130.7), CH (129.2), CH (129.1), CH (113.7), CH_2 (100.0), CH_2 (74.3), CH_2 (72.5), CH_2 (72.46), CH_2 (68.9), CH_3 (55.2), CH (47.8), CH (47.7), CH (44.3), CH (44.1), CH (44.0), CH (43.2), CH (41.4), CH (41.3), CH (39.6), CH (38.7), CH (38.1), CH_2 (33.6), CH_2 (29.9). HRMS (ESI) m/z calculated for **16** $[M+Na]^+$ 561.2981, found 561.2968.

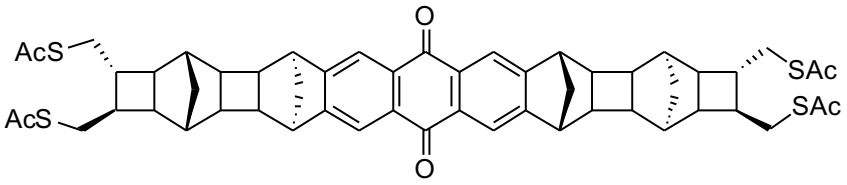


Preparation of 17. To a solid portion of **16** (0.800 g, 1.4861 mmol) was added a solid portion of benzoquinone (0.08026 g, 0.74306 mmol) in a pressure tube. The mixture was then dissolved in dry toluene (4 mL). The solution mixture was then degassed by bubbling argon for 20 min before the pressure tube was sealed and heated at 145° C for 4 days. The solvent was then evaporated under reduced pressure to give a pale yellow solid. The solid was subjected to column chromatography. (eluent 2:98 ethylacetate/DCM) to furnish the title compound **17** as pale yellow colour (0.810 g, 92%). The title compound contains a mixture of isomers that were not separated at this stage. The separation of the isomers was left to a later stage. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.16 (d, *J* = 8.4 Hz, 8H), 6.78 (d, *J* = 8.4 Hz, 8H), 4.33 (s, 8H), 3.72 (s, 12 H), 3.50-3.20 (m, 8H), 2.48 (s, 2H), 2.32 (m, 2H), 1.85 (m, 1H), 1.75-1.65 (m, 10 H), 1.65-1.60 (m, 6H), 1.48-1.15 (m, 10H), 1.13-1.08 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2 (Cq), 132.0 (Cq), 130.7 (Cq), 129.9 (CH), 114.1 (CH), 113.5 (CH), 74.1 (CH_2), 72.8(CH_2), 68.5 (CH_2), 55.2 (CH_3), 55.1 (CH_3), 47.5 (CH), 47.1 (CH), 46.8(CH), 44.7 (CH), 44.3 (CH), 44.1 (CH), 43.8 (CH), 43.2 (CH), 40.8 (CH_2), 41.5 (CH_2), 38.8 (CH), 38.2 (CH), 35.4(CH), 35.1(CH), 33.4 (CH), 31.3 (CH_2), 31.0 (CH_2), 30.8 (CH_2). HRMS (ESI) m/z calculated for **17** $[M+Na]^+$ 1207.6275 , found 1207.6260.



Preparation of 18. To a solution of **17** (810 mg, 0.684 mmol) dissolved in DCM (40 mL) and water (5 mL) in a pressure tube was added a solid portion of DDQ (650 mg, 2.860 mmol). The resulting brown reaction mixture was heated for 3 h at 70 °C after which it was cooled to room temperature. 1,4 cyclohexadiene (1 mL) was then added and the reaction mixture was left stirring for 30 min at room temperature. The solvents were then removed under reduced pressure furnishing a brown solid which was not purified any further. The brown solid was then redissolved in anhydrous pyridine (30 mL) and the mixture was cooled in an acetone-ice bath to − 10° C. Tosyl chloride (1.50 g, 7.867 mmol) was then added in small portions under argon. The reaction mixture was left at − 10 °C for 24 h after which ice cold DCM was added and the mixture was transferred to a separatory funnel. The organic phase was washed with 2 M HCl (5×100 mL) and then washed with a saturated solution of $NaHCO_3$, water (2× 100 mL) and dried with sodium sulphate. The solvent was then evaporated under reduced pressure to furnish an orange coloured solid. The solid was subjected to column chromatography eluent (100% DCM to elute the excess tosyl chloride and the excess p-methoxy benzylaldehyde and then (10:90 ethyl acetate-DCM to furnish the title compound as yellow solid. (433 mg, overall yield: 48%). Note that several fractions which correspond to the isomers of the same title

compound (very close Rf values) could be separated on the column at this stage. However, these fractions were combined and taken to the next step and the separation of isomers was left to a later stage. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.2 Hz, 8H), 7.27 (d, *J* = 8.2 Hz, 8H), 4.11-3.88 (m, 4H), 3.85-3.70 (m, 4H) 3.20-3.15 (m, 2H), 2.65-2.55 (m, 2H), 2.31-2.24 (m, 18H), 1.95-1.70 (m, 17 H), 1.47-1.15 (m, 13H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.1 (Cq), 133.1 (Cq), 130.0 (CH), 128.1 (CH), 72.7 (CH_2), 68.4 (CH_2), 46.3 (CH_2), 42.7 (CH), 41.5 (CH), 40.8 (CH), 40.3 (CH), 38.0 (CH), 36.2 (CH), 30.1 (CH_2), 29.8 (CH_2), 21.6 (CH_3). HRMS (ESI) m/z calculated for **18** $[M+Na]^+$ 1343.4329 , found 1343.4339



Preparation of 19. To a solution of **18** (400 mg, 0.303 mmol) in anhydrous DMSO (20 mL) was added a solid portion of potassium thioacetate (300 mg, 2.628 mmol) under argon. The solution mixture was heated at 70 °C for 24 h after which it was cooled to room temperature. The solution mixture was then transferred to a separation funnel where DCM (100 mL) and water (100 mL) were added. The organic phase was further washed with water (5 × 100 mL), dried with sodium sulphate and the solvent was evaporated under reduced pressure to furnish a pale yellow solid. The solid was not purified further and was dissolved in anhydrous 1,1,2,2-tetrachloroethane (15 mL) in a pressure tube. A solid portion of DDQ (300 mg, 1.31 mmol) was then added under argon and the solution mixture was heated at 145 °C for 36 h after which was cooled to room temperature. 1,4-cyclohexadiene (1 mL) was then added and the reaction mixture was left stirring for 30 min at room temperature. The solvent was then evaporated to furnish a dark brown solid. The solid was subjected to column chromatography eluent (100% DCM) and then (5:95 ethyl acetate-DCM solvent mixture) to give a mixture of the *syn* and *anti* isomers. (103.1 mg, overall yield: 48 %). The product was further subjected to column chromatography in order to separate the isomers eluent (1:99 ethyl acetate-DCM solvent mixture to furnish two fractions: a higher Rf; *syn* isomer **19'** (67%, 69.07 mg).^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (s, 4H), 3.25 (s, 4H), 3.10-2.90 (m, 4 H), 2.85-2.70 (4H), 2.28-2.12 (m, 18 H), 2.05-1.85 (m, 4H), 1.80-1.40 (m, 22 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.9 (Cq), 183.7 (Cq), 153.5 (Cq), 132.4 (Cq), 119.2 (CH), 46.2 (CH), 43.2 (CH), 42.6 (CH), 42.2 (CH_2), 41.8 (CH), 41.4 (CH), 41.2 (CH), 38.9 (CH), 37.9 (CH), 34.9 (CH_2), 30.7 (CH_3), 30.0 (CH_2), 27.8 (CH_2). HRMS (ESI) m/z calculated for the *syn*-isomer **19'** $[M+Na]^+$ 951.2857 , found 951.2865.

and the title lower Rf *anti* isomer **19** (33 %, 34.02 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (s, 4H), 3.27 (s, 4H), 3.10-2.90 (m, 4 H), 2.85-2.72 (4H), 2.28-2.15 (m, 18 H), 2.05-1.85 (m, 4H), 1.80-1.40 (m, 22 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.1 (Cq), 184.2 (Cq), 153.6 (Cq), 132.7 (Cq), 119.4 (CH), 46.2 (CH), 43.2 (CH), 42.6 (CH), 42.3 (CH_2), 41.8 (CH), 41.4 (CH), 41.3 (CH), 38.9 (CH), 37.9 (CH), 34.9 (CH_2), 30.7 (CH_3), 29.9 (CH_2), 27.9 (CH_2). HRMS (ESI) m/z calculated for **19** $[M+H]^+$ 929.3038, found 929.3038.

The isolation of the *anti*-isomer was confirmed by an X-ray crystal structure (Figure S12).

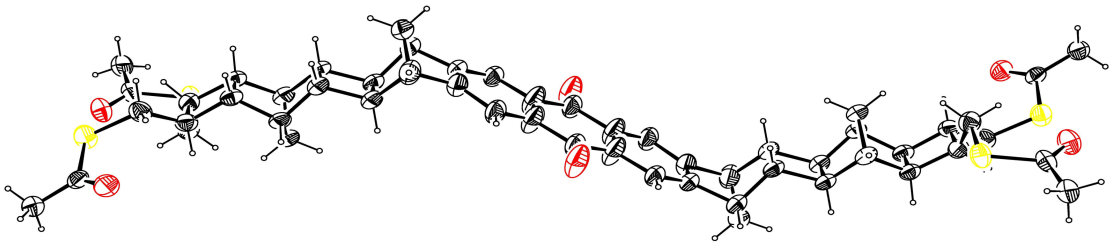
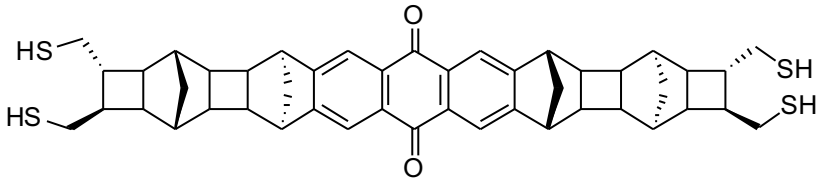


Figure S12. X-ray crystal structure as ORTEP format of compound **19**. The X-ray measurements were carried out using Synchrotron beams (Australian Synchrotron) on a MX3 instrument. Crystals were grown from a mixture of DCM-methanol solvent. CCDC-851607 contains the supplementary crystallographic data. These data can be obtained free from charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.



Preparation of 20. To a solution of **19** (30 mg, 0.032 mmol) in degassed DCM (10 mL) and degassed methanol (40 mL) was added concentrated HCl (200 μL). The mixture was further degassed by bubbling argon for 10 min. The reaction mixture was then brought to reflux under argon for 48 h after which it was allowed to cool to room temperature. Water (100 mL) was then added and the two layers separated. The organic layer was further washed with saturated sodium bicarbonate (2×100 mL), water (2×100 mL), dried by sodium sulphate and evaporated to dryness furnishing the title compound **20** as a yellow solid (22.7 mg, 93 %).^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (s, 4H), 3.26 (s, 4H), 2.68-2.50 (m, 9H) 2.40-2.30 (m, 6H), 2.20-1.90 (m, 10H), 1.85-1.60 (m, 12 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.1 (Cq), 153.6 (Cq), 132.6 (Cq), 119.2 (CH), 46.2 (CH), 45.6 (CH), 43.0 (CH), 42.6 (CH), 42.3 (CH_2), 41.9 (CH), 41.6 (CH), 38.5 (CH), 37.7 (CH), 30.8 (CH_2), 30.2 (CH_2), 23.4 (CH_2).

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