Optimizing the Reduction Potential of Sulfonamides on PAMAM Dendrimers

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ABSTRACT

p-Toluenesulfonamide serves as an important functional group to protect alkyl amines. However, the electrochemical deprotection of sulfonamides requires relatively high reduction potentials (-2.4V vs SCE) that would interfere with other functional groups. Previous investigations suggest that methods are available to decrease the reduction potential, but no systematic investigation has been conducted that evaluates the reduction potential as a function of aryl-substitution, mediator, or multi-arm grafting. Cyclic voltammetric studies of a library of bis-sulfonamides bearing different aryl substituents in DMF reveals that *p*-NO_2 substituted bis-sulfonamide has the lowest reduction potential. Further investigations aimed at lowering the cathodic potential with polycyclic aromatic hydrocarbon mediators display negligible or no impact. This optimised condition was successfully applied to fully *p*-nitrobenzenesulfonyl protected generation zero and generation one polyamidoamine dendrimers ($G_{0.0}$-PAMAM-Ns and $G_{1.0}$-PAMAM-Ns), demonstrating successful amine protection and deprotection on dendrimers for the first time.

Keywords: bis-sulfonamide, cyclic voltammetry, PAMAM dendrimer, structure activity relationship

INTRODUCTION

Amine functional groups serve as initiators for many crosslinking reactions in plastic thermosets, adhesives, and biologically active substances. To control initiation and propagation events, various protecting groups are available to shield the primary amine's nucleophilic properties. Among the various protecting groups, the *p*-toluenesulfonyl group is an expedient amine protecting group, well known for its ease of introduction and simple workup. The resulting sulfonamides are crystalline solids and stable towards a wide range of synthetic environments. However, removal of the N-tosyl group requires harsh reducing environments that need to be carefully chosen to prevent non-specific side reactions. Recently several milder reductions have been advanced with $NaBH_4$ mediated photolysis,[1] treatment with SmI_2,[2] $Ni(acac)_2$/*i*PrMgCl,[3] low-valent titanium,[4, 5] Mg/ MeOH,[6] $LiEt_3BH$,[7] Bu_3SnH/AIBN,[8] and electrochemical reduction. Exploitation of the latter would allow microelectronic interfacing of thermoset resins for in-line bonding and manufacturing applications. Electrochemical reactions have several advantages when compared to chemical initiators, such as (i) mild reaction conditions at room temperature and atmospheric pressure, (ii) high atom economy and produces little to no waste, (iii) only reagent required is electric current, and (iv) it offers functional group tolerance and voltage-dependent chemoselectivity.

Electrochemical deprotection of *p*-toluenesulfonamide occurs under mild reaction conditions with the amine formation in high yield. One disadvantage is the requirement of a high voltage (-2.4V vs SCE), which may reduce or decompose other functional groups. Electrochemical methods are thus required for amine deprotection at low cathodic potentials of -0.5 to -1.5 V. Herein, structure activity relationships of bis-sulfonamides are investigated with respect to the proton donor (AcOH), polycyclic mediators, and aromatic substitution. *P*-NO_2 substituted bis-sulfonamide displays the lowest cathodic potential value in the presence of AcOH.

The CV measurements of branched polyamidoamine (PAMAM) dendrimers protected with *p*-NO_2 sulfonamide were then performed under this optimised condition. PAMAM dendrimers are molecules that have been utilized in electro-active adhesive biomedical applications (Scheme S1). PAMAM dendrimers with several amine functional groups on their surface have the advantage of being able to be grafted with other molecules. In a two-part adhesive formulation with epoxy resins, PAMAM dendrimers allow rapid gelation and strong bonding,[9, 10] although they suffers from limited manipulation. On the other hand, PAMAM derived one-pot adhesives suffer from weak adhesion strength.[11-13] It is hypothesised that aryl sulfonyl functionalised PAMAM should be stable in presence of an epoxy resin and therefore, can be used to formulate one-pot structural or bioadhesives. Electrochemical deprotection of the aryl sulfonyl functionalised PAMAM amino groups can then result in strong bonding upon crosslinking with the electrophilic epoxy resin.

MATERIALS and METHODS

General Methods

All experiments were carried out in dried glassware. ^{1}H NMR (400 MHz, 500 MHz) and ^{13}C NMR (100 MHz, 125 MHz) spectra were recorded on Bruker AVANCE 400 MHz and 500 MHz instruments in the deuterated solvent C_2D_6SO. Chemical shifts are given in parts per million (ppm, d) based on the middle peak of the solvent signal (^{1}H NMR, δ = 2.50 for C_2D_6SO; ^{13}C NMR, δ = 39.51 for C_2D_6SO) as an internal standard. The J values are given in Hz. Multiplicities are indicated as ‘s' (singlet), ‘d' (doublet), ‘t' (triplet), ‘q' (quartet), ‘m' (multiplet) and ‘brd' (broad dublet). MS data were obtained using Agilent 6850 GC equipped with an Agilent 5973 MSD working under standard conditions and an Agilent HP5-MS column, a Bruker Daltonics Ion Trap MS Esquire 3000 Plus equipped with APCI (atmospheric pressure chemical ionization) analyzed by Xcalibur software (Thermo Fisher Scientific), Helium gas flow 30 mL min^{-1}, column temperature from 160 to 280 ^{o}C. High resolution mass spectra analysis (HR-MS) was obtained on LTQ XL Orbitrap ETD by direct injection electrospray ionization (ESI) sources using the time-flight mass spectrometry. Analytical thin layer chromatography (TLC) was performed on aluminium sheets with silica gel 60 F254. Visualization was accomplished with UV light. All reactions were carried out under nitrogen. Evaporation of solvents was performed at reduced pressure using a rotary evaporator. All reagents and solvents were purchased from Aldrich and used without further purification unless otherwise indicated.

Cyclic Voltammetry (CV)

Voltammetric measurements were performed using a Metrohm Autolab PGSTAT302N potentiostat in a three-electrode setup. A 3 mm diameter planar glassy carbon disk (Metrohm) was used as a working electrode in conjunction with a platinum wire counter electrode

(Metrohm) and SCE reference electrode (filled with 3 M KCl water solution). The cyclic voltammetric data were recorded in DMF solution with 0.1 M electrolyte, at the scan rate 0.1 V/s. All voltammetric experiments were conducted under an argon atmosphere, at room temperature in a Faraday cage. Prior to each scan, the working electrode was cleaned by polishing with alumina oxide (grain size 0.3 μm) slurry on a Buehler Ultra-pad polishing cloth, rinsing with ethanol, and then drying with a lint free tissue.

Preparation of N-arenesulfonamides

General Procedure for Synthesis:

Synthesis of 2a: To a stirred solution of ethylenediamine (0.5 g, 8.3 mmol, 1.0 equiv) in pyridine (10 mL) was added 4-methoxybenzenesulfonyl chloride (3.53 g, 17.08 mmol, 2.05 equiv) portion wise over a period of 30 min. at 0 °C under nitrogen atmosphere. After being stirred 24 h at room temperature, the reaction mixture was poured into water (50 mL). The resulting solids were collected by filtration, washed sequentially with 1N aqueous HCl, water, diethyl ether, and dried *in vacuo* to give the title compound (2.24 g, 67%) as a light pink solid.

***N,N'*-(ethane-1,2-diyl)bis(4-methoxybenzenesulfonamide) (2a).** ^{1}H NMR (500 MHz, C_2D_6SO) δ 7.67-7.62 (m, 4H), 7.52 (brs, 2H), 7.06=7.11 (m, 4H), 3.84 (s, 6H), 2.72–2.65 (m, 4H); ^{13}C NMR (100 MHz, C_2D_6SO) δ 162.14, 131.81, 128.57, 114.32, 55.60, 42.09; HRMS (ESI) m/z calcd for $C_{16}H_{21}N_2O_6S_2$ $[M+H]^+$ = 401.0841; found 401.0850.

***N,N'*-(ethane-1,2-diyl)bis(4-methylbenzenesulfonamide) (2b).** ^{1}H NMR (500 MHz, C_2D_6SO) δ 7.64-7.55 (m, 6H), 7.37 (d, *J* = 8.0 Hz, 4H), 2.73–2.66 (m, 4H), 2.38 (s, 6H); ^{13}C NMR (100 MHz, C_2D_6SO) δ 142.71, 137.34, 129.63, 126.44, 42.12, 20.93; HRMS (ESI) m/z calcd for $C_{16}H_{21}N_2O_4S_2$ $[M+H]^+$ = 369.0943; found 369.0940.

***N,N′*-(ethane-1,2-diyl)bis(4-chlorobenzenesulfonamide) (2c).** ^{1}H NMR (400 MHz, C_2D_6SO) δ 7.82 (brs, 2H), 7.76-7.70 (m, 4H), 7.68-7.62 (m, 4H), 2.75 (brs, 4H); ^{13}C NMR (100 MHz, C_2D_6SO) δ 139.06, 137.36, 129.37, 128.36, 42.09; HRMS (ESI) m/z calcd for $C_{14}H_{15}N_2O_4S_2Cl_2$ $[M+H]^+$ = 408.9850; found 408.9841.

***N,N′*-(ethane-1,2-diyl)bis(4-(trifluoromethyl)benzenesulfonamide) (2d).** ^{1}H NMR (400 MHz, C_2D_6SO) δ 8.01 (brs, 2H), 7.96 (s, 8H), 2.84–2.75 (m, 4H); ^{13}C NMR (100 MHz, C_2D_6SO) δ 144.17, 132.72, 132.39, 132.07, 131.75, 127.39, 126.48, 126.45, 124.79, 123.88, 122.08, 42.17; HRMS (ESI) m/z calcd for $C_{16}H_{15}N_2O_4S_2F_6$ $[M+H]^+$ = 477.0377; found 477.0365.

***N,N′*-(ethane-1,2-diyl)bis(pyridine-3-sulfonamide) (2e).** ^{1}H NMR (400 MHz, C_2D_6SO) δ 8.91 (d, *J* = 1.4 Hz, 2H), 8.85 (d, *J* = 4.68 Hz, 2H), 8.13 (d, *J* = 8.0 Hz, 2H), 7.99 (brs, 2H), 7.68-7.58 (m, 2H), 2.89–2.79 (m, 4H); ^{13}C NMR (100 MHz, C_2D_6SO) δ 153.11, 146.95, 136.56, 134.47, 124.30, 42.21; HRMS (ESI) m/z calcd for $C_{12}H_{15}N_4O_4S_2$ $[M+H]^+$ = 343.0535; found 343.0551.

***N,N′*-(ethane-1,2-diyl)bis(4-cyanobenzenesulfonamide) (2f).** ^{1}H NMR (400 MHz, C_2D_6SO) δ 8.11-8.01 (m, 6H), 7.93-7.87 (m, 4H), 2.83–2.75 (m, 4H); ^{13}C NMR (100 MHz, C_2D_6SO) δ 144.33, 133.45, 127.18, 117.66, 114.95, 42.20; HRMS (ESI) m/z calcd for $C_{16}H_{15}N_4O_4S_2$ $[M+H]^+$ = 391.0535; found 391.0524.

***N,N′*-(ethane-1,2-diyl)bis(4-nitrobenzenesulfonamide) (2g).** ^{1}H NMR (500 MHz, C_2D_6SO) δ 8.42-8.36 (m, 4H), 8.14 (t, *J* = 5.5 Hz, 2H), 8.02-7.96 (m, 4H), 2.86–2.80 (m, 4H); ^{13}C NMR (100 MHz, C_2D_6SO) δ 149.57, 145.79, 128.03, 124.59, 42.27; HRMS (ESI) m/z calcd for $C_{14}H_{15}N_4O_8S_2$ $[M+H]^+$ = 431.0331; found 431.0312.

General Procedure for Synthesis of $G_{0.0}$-PAMAM-Ns (4) and $G_{1.0}$-PAMAM-Ns (6):

Synthesis of 4: To a stirred solution of $G_{0.0}$-PAMAM (202 mg, 0.39 mmol, 1.0 equiv) in DMSO (3 mL) was added triethylamine (0.54 mL, 3.91 mmol, 10.0 equiv) *p*-nitrobenzenesulfonyl chloride (520 mg, 2.35 mmol, 6.0 equiv) portion wise over a period of 5 h at room temperature under nitrogen atmosphere. The resulting mixture was stirred and heated at 42 °C for 30 h. It was cooled to room temperature, poured dropwise into ether (50 mL) while stirring vigorously. The Et_2O layer was decanted off and the yellow precipitation was triturated with a mixture of MeOH-Et_2O (1:20; 50 mLx3) and dried *in vacuo* to give the title compound (319 mg, 65%) as a yellow solid.

$G_{0.0}$-PAMAM-Ns (4). ^{1}H NMR (400 MHz, MeOD) δ 8.38 (d, *J* = 8.68 Hz, 8H), 8.06 (d, *J* = 8.68 Hz, 8H), 3.26 (t, *J* = 6.0 Hz, 8H), 3.03 (t, *J* = 5.92 Hz, 8H), 2.88-2.73 (m, 8H), 2.65-2.59 (m, 4H), 2.43-2.30 (m, 8H).

$G_{1.0}$-PAMAM-Ns (6). ^{1}H NMR (400 MHz, MeOD) δ 8.28 (d, *J* = 8.84 Hz, 16H), 8.00 (d, *J* = 8.84 Hz, 16H), 3.27-3.18 (m, 24H), 3.00-2.91 (m, 16H), 2.81-2.69 (m, 24H), 2.60-2.52 (m, 12H), 2.40-2.27 (m, 24H).

RESULTS and DISCUSSION

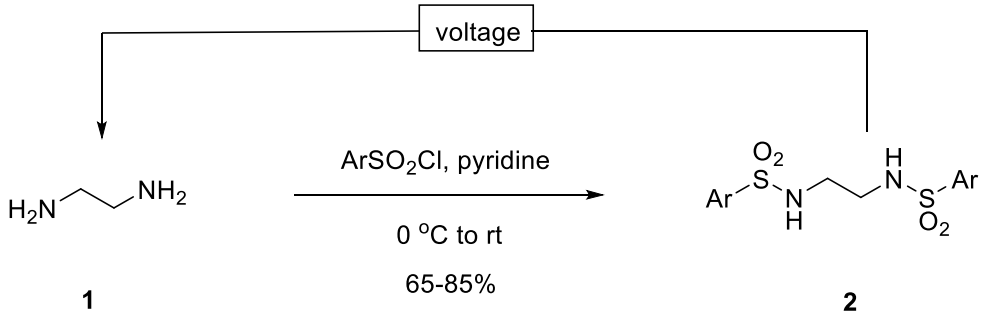
Scope of the SAR study

Electrochemical deprotection of amine-protected sulfonamides would allow regulation of reactions where amines initiate polymerization. Microprocessor control of such polymerization initiation is an unmet demand in the new Industry 4.0 paradigms. This requires a balance of shelf stability (no spontaneous deprotection) yet relying on a low reduction potential to limit side reactions of other resin functional groups. Towards this optimization, a model diamine of ethylenediamine was protected with a library of bis-sulfonamides. The first structure activity relationship (SAR) focuses on the cathodic potential

required with respect to electron withdrawing/donating aryl sulfonyl groups. It is hypothesized that a selection of seven aryl substituents with varying electronic properties will give a range of activation voltages towards chemoselectivity. Cyclic voltammetry on glassy carbon electrodes was used to assess the cathodic potential with respect to the standard calomel electrode (SCE). After optimization, inclusion of polycycle mediators was used to evaluate further chemoselectivity and kinetics. The optimization extended from ethylenediamine to protected tetra-amine and octaamine dendrimers ($G_{0.0}$ and $G_{1.0}$-PAMAM) for further evaluation of the desulfonylation process for compounds having higher number of sulphonamide protecting groups.

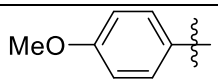
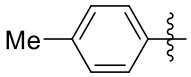
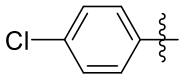
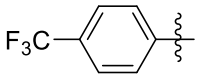
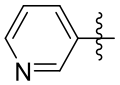
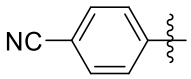
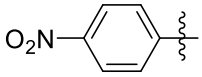
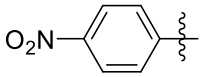
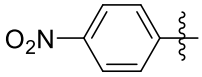
Synthesis of bis-sulfonamides and nosyl protected PAMAM dendrimers

All the bis-sulfonamides (**2a-2g**) were prepared in one step by stirring a pyridine solution of the ethylenediamine at room temperature for 24 h under argon atmosphere (**Scheme 1**).[14] After completion, the reaction mixture was poured into a large volume of water and the precipitated product was washed with diethyl ether and dried under vacuum. All the bis-sulfonamides were characterized by ^{1}H, ^{13}C and high-resolution mass spectroscopy analysis. Yields of various bis-sulfonamides are summarised in **Table 1**.



Scheme 1. Synthesis of **bis-sulfonamides**: Reagents and Conditions: (a) $ArSO_2Cl$, Pyridine, 0 °C to rt, 8-16 h, 65-84%.

Table 1. Preparation of bis-sulfonamides and nosyl protected $G_{0.0}$-PAMAM and $G_{1.0}$-PAMAM and corresponding cathodic reduction potentials.

Entry	Substrate	Ar	Yield (%)	Product	E_p, V
1			67	**2a**	-2.53
2			73	**2b**	-2.42
3			73	**2c**	-2.07
4	**1**		81	**2d**	-2.03
5			65	**2e**	-1.89
6			85	**2f**	-1.76
7			71	**2g**	-0.93
8	$G_{0.0}$-PAMAM (**3**)		65	**4**	-0.93
9	$G_{1.0}$-PAMAM (**5**)		61	**6**	-0.93

E_p = peak potential

Synthesis of $G_{0.0}$-PAMAM-Ns and $G_{1.0}$-PAMAM-Ns are illustrated in **Scheme S1**. First, synthesis of $G_{0.0}$-PAMAM-Ns was attempted by stirring a pyridine solution of $G_{0.0}$-PAMAM with *p*-NO_2-benzene sulfonyl chloride at room temperature for 24 h, following the procedure described for the synthesis of **2a**. After 24 h, the product precipitated out of the pyridine solution and ^{1}H NMR analysis of the purified product revealed that the reaction resulted in 52% capping of end amines. In order to increase solubility of the partially protected dendrimer, the reaction was performed in a solution of DMF-DMSO (4:3) using pyridine as a base and stirring for 24 h at room temperature. Though the capping improved to 69%, it did not result in complete capping of the terminal amine groups. Next, the sulfonylation was

carried out in DMSO solution of $G_{0.0}$-PAMAM using a stronger base (Et_3N) and heating the reaction mixture at 42 ^oC for 24 h. The ^1H NMR analysis of the purified product revealed that the $G_{0.0}$-PAMAM dendrimer was fully end capped. This optimised reaction condition was used for the terminal amino group sulfonylation of $G_{1.0}$-PAMAM.

CYCLIC VOLTAMMETRY INVESTIGATION

Effect of AcOH on cathodic reduction potential in different electrolytes

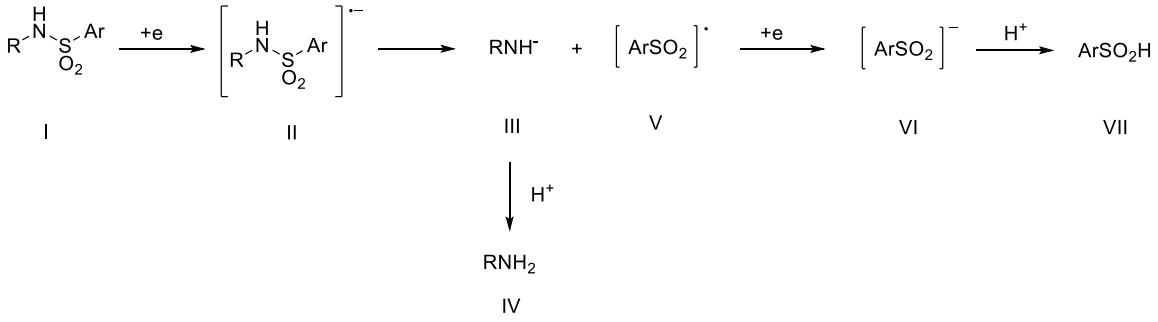
Electron transport through the solution requires a medium of high conductivity, whereas most organic solvents are inherently nonconductive. To perform electrochemical reactions or cyclic voltammetric measurements in an organic or aqueous solvent, addition of an electrolyte is essential. The electrolyte ions enable ionic conductivity of the solution to support the flow of current due to reactions at the electrodes. Therefore, the rate and selectivity of an electrochemical transformation may depend on the electrolyte selection.

Bis-*p*-toluenesulfonamide (**2b**) was chosen as the model compound for CV studies to investigate the effect of a proton donor in presence of different electrolytes. Dimethylformamide (DMF) or acetonitrile (MeCN) and various electrolytes (Bu_4NPF_6, Bu_4NBF_4, Bu_4NClO_4, Bu_4NHSO_4, Bu_4NI, Et_4NBr) are frequently used for electrochemical desulfonylation of N-arenesulfonamides.[15, 16] However, DMF gives higher solubility of sulfonamides compared to MeCN. All CV measurements were performed in DMF with 2.0 mmol substrate, 0.1 molar supporting electrolyte concentration and 4 molar equivalents of AcOH using a GC working electrode, SCE reference electrode and Pt counter electrode. The results of CV measurements in the presence and absence of AcOH in different electrolyte are displayed in **Figure S1a-f**. The enhancement of the cathodic peak height in the presence of a proton donor is ascribed to the conversion of an amide ion intermediate (III in **Scheme 2)** to the final amine, leading to complete consumption of the sulfonamide.[15] Based on these

observations, it was decided to add a proton donor (AcOH) using Et_4NBr as electrolyte for the subsequent investigations.

Effect of aryl substituent on cathodic reduction potential

Electrochemical deprotection of sulfonamide to amine proceeds via the formation of an amide anion intermediate (III) which abstracts a proton from a proton donor leading to the formation of the amine (IV) (**Scheme 2**).[15]



Scheme 2. Reaction steps for sulfonamide deprotection

Ease of electrochemical reduction of sulfonamide (I) depends on the electronic nature of the aryl substituent present. The first electron transfer leads to the formation of sulfonamide radical anion intermediate (II) and is proposed to be the rate determining step for this reaction. [15] An aryl substituent with higher electron affinity stabilizes the intermediate sulfonamide radical anion (II) more than a substituent with lower electron affinity. Thus, electron withdrawing aryl substituents are expected to display lower cathodic reduction potentials than electron donating aryl substituents. Taking this into consideration, electrochemical behavior of a library of bis-sulfonamides with different aryl substituents were investigated. The values of the cathodic peak potentials obtained from the cyclic voltammetry study are summarized in **Table 1**. **Figure 1** displays voltammograms of compounds having the highest (**2a**), moderate (**2d**) and lowest (**2g**) cathodic peak potential values. Voltammograms of the other 4 sulfonamides are shown in **Figure S2**. The reduction

peaks of all bis-sulfonamides appear to be chemically irreversible in the sense that only a forward reduction peak is observed, and no reverse oxidation peak is seen when the scan direction is reversed. The reduction process are exhibited within the range of -1.76 to -2.53V, except for **2g** that has a significantly lower reduction peak at -0.93V. Reduction peaks of sulfonamides **2a** and **2b** are preceded by a small shoulder. **Table 1** shows that sulfonamides with *p*-OMe (**2a**) and *p*-CH_3 (**2b**) benzene substitution have cathodic peaks at -2.53V and -2.42V respectively. The higher values of cathodic reduction potential with electron donating aryl substituents is ascribed to the lower electron affinity of the sulfonamide (I). Thus, electron donating aryl substituents (e.g. CH_3, OMe) shifts the cathodic potential to more negative values. Alternatively, sulfonamides with electron withdrawing substituents have higher affinity for electron transfer in the first step of desulfonylation process. The data in **Table 1** indicate that electron withdrawing substituents (CN, Cl, CF_3, pyridine, NO_2 etc.) shifts the cathodic peak to a less negative value. *p*-OMe being the strongest electron donating substituent exhibits the highest (most negative) cathodic potential at -2.53V while *p*-NO_2 being the strongest electron withdrawing substituent exhibits lowest value at -0.93V.

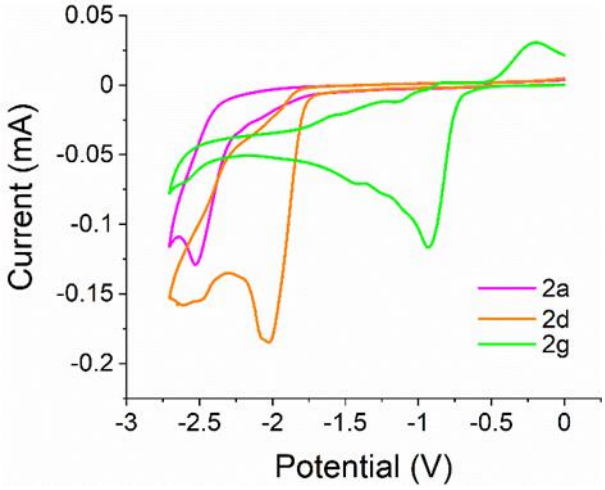


Figure 1. Cyclic voltammograms of **2a, 2d** and **2g** (2 mM) with Et_4NBr/DMF (0.1 M) and AcOH (8 mM) using 3 mm diameter GC working electrode vs SCE at 298±2 K in a Faraday cage. Scan rate – 0.1 V s^{-1}.

Effect of mediator on cathodic reduction potential

Mediators in general help to reduce (or oxidize) a functional group at a potential lower than that needed were the electrochemical reaction is carried out directly, thereby improving the yield and consuming less energy. Mediators act as catalysts and can be reused.

Having obtained the lowest value of the reduction potential for the *p*-nitro substituent (**2g**), the addition of a mediator was attempted to further improve the efficiency. Polycyclic aromatic hydrocarbon mediators reportedly play an effective role in electrochemical detosylation of sulfonamides by lowering the cathodic potential and by increasing the electrolysis yield.[17-19] The influence of three different mediators - anthracene, naphthalene and pyrene on the electrochemical behavior of **2g** were studied by adding in one and two molar equiv versus a control (no mediator). **Figure 2** displays the influence of one and two molar equivalent of anthracene on the electrochemical behavior of **2g** while **Figure S3a-b** displays the same effect in the presence of naphthalene and pyrene. From these voltammograms, it can be seen that there is a negligible effect on either the increase in reduction peak current or shifting of the cathodic potential of sulfonamide **2g** in the presence of any of these polycyclic aromatic hydrocarbon mediators. A similar result was observed for sulfonamide **2a** which has an electron donating *p*-OMe aryl substituent (**Figure S4)**. Thus, it can be concluded that polycyclic aromatic hydrocarbon mediators have negligible impact on cathodic peak currents and voltammetric potentials of sulfonamides bearing aryl substituents of varying electronic properties.

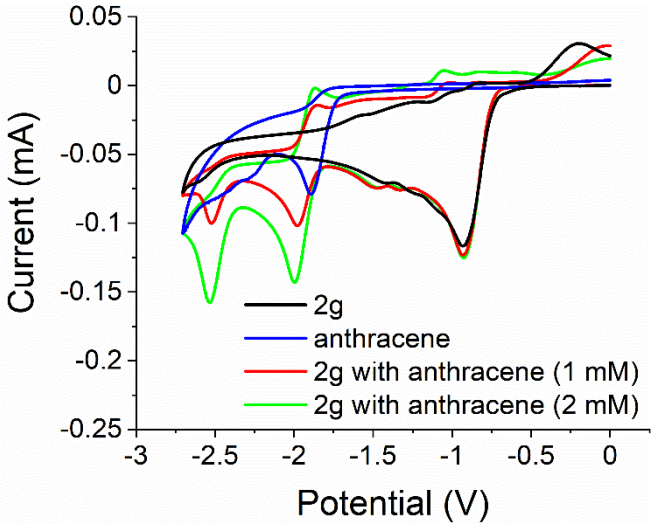


Figure 2. Cyclic voltammograms of **2g** (2 mM) with anthracene (1 mM, 2 mM), Et_4NBr/DMF (0.1 M), and AcOH (8 mM) using 3 mm diameter GC working electrode vs SCE at 298±2 K in a Faraday cage. Scan rate – 0.1 V s^{-1}.

Sulfonamide protected PAMAM dendrimers have comparable cathodic potential

This investigation was carried out to compare electrochemical behavior of aryl sulfonyl protected diamines with that of polyamines such as tetra- and octa-amines and simultaneously to examine electrochemical behavior of aryl sulfonyl protected polyamidoamine (PAMAM) dendrimers. Polyamidoamines $G_{0.0}$-PAMAM and $G_{1.0}$-PAMAM were chosen for this study as they have four and eight terminal amines (-NH_2) respectively. Treatment of $G_{0.0}$-PAMAM and $G_{1.0}$-PAMAM with *p*-NO_2-benzene sulfonyl chloride in the presence of a base provide nosyl protected dendrimers **4** and **6 (**$G_{0.0}$-PAMAM-Ns and $G_{1.0}$-PAMAM-Ns). A cyclic voltammetric investigation of these two substrates were performed in DMF solution with 1.0 mmol **4** (and 0.5 mmol **6**), 0.1 molar supporting electrolyte concentration and 8 molar equivalents of AcOH (16 molar equivalents of AcOH for substrate **6**) using a GC working electrode, SCE reference electrode and Pt counter electrode and the cathodic peak potentials were compared with that of **2g**. A comparison of the voltammograms indicated that

compounds with two, four and eight sulfonamides have similar values of cathodic reduction potential (~ -0.93V) (**Figure 3)**. This investigation established that compounds with different

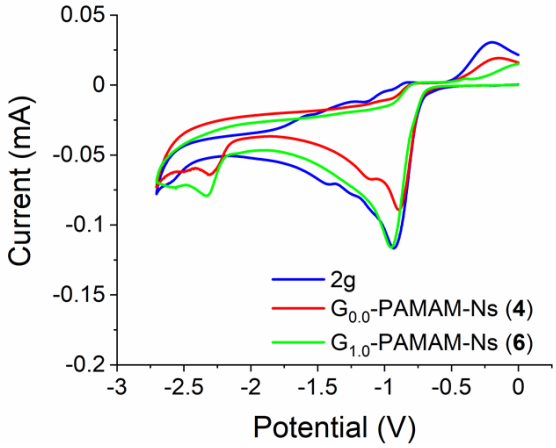


Figure 3. Cyclic voltammograms of **2g**, **4** and **6** (2mM, 1 mM and 0.5 mM) with Et_4NBr/DMF (0.1 M) and AcOH (8 mM) using 3 mm diameter GC working electrode vs SCE at 298±2 K in a Faraday cage. Scan rate – 0.1 V s^{-1}.

numbers of nosyl protected amines will undergo sulfonamide deprotection even on macromolecular dendrimers. A controlled potential electrolysis (CPE) experiment was carried out for dendrimer **4**. Approximately 8 electrons (**Figure 4a**) were transferred during the exhaustive reduction process. The CV response (**Figure 4b**) before CPE (black line) and after CPE (blue line) shows a significant decreased in the cathodic peak current. The result further supports that PAMAM dendrimers could undergo sulfonamide deprotection in the given experimental conditions during bulk electrolysis.

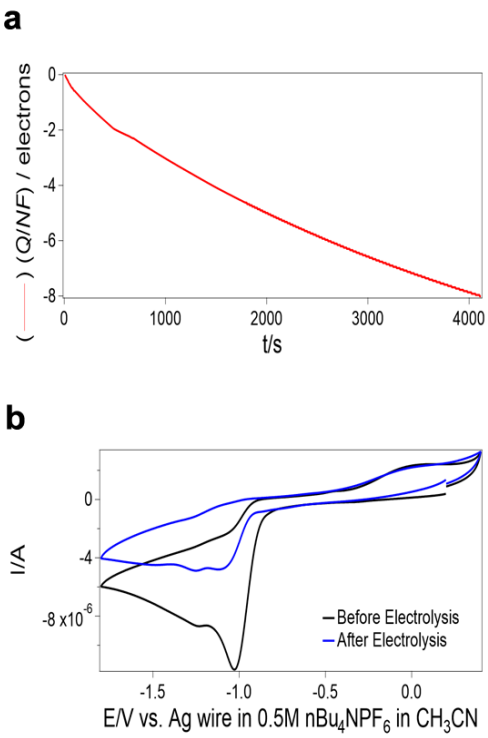


Figure 4. Coulometric data (no. of electrons against time) and CV response for reductive electrolysis of **4** (1 mM) in Et_4NBr/DMF (0.1 M), and 10 equiv. of AcOH (10 mM) using 1 mm diameter GC working electrode vs Ag wire in 0.5 M nBu$_4$NPF$_6$/CH$_3$CN at 298±2 K. Scan rate – 0.1 V s-1. (a) Coulometric data for reductive CPE. (b) CV response before CPE (Black line) After CPE (Blue line).

CONCLUSION

A multiparameter SAR study was carried out to obtain the minimum reduction potential value of bis- or polysulfonamides, which may be exploited as microprocessor controls of polymerization initiation. The reduction potential of commonly used epoxy resin is ~ -2.2V.[20] CV investigations of bis-sulfonamide **2b** reveals that the addition of a proton donor (AcOH) is essential as it enhances the cathodic peak currents for desulfonylation. A structure activity relationship (SAR) analysis by comparing voltammograms of 7 bis-sulfonamides bearing substituents of varying electronic properties revealed that *p*-NO_2 substituted bis-sulfonamide has the lowest reduction potential (-0.93V). Therefore, plastic resins containing

bis- or polysulfonamide should be shelf stable up to this potential. This investigation can be exploited as a guide for investigation of other protected nucleophiles. For the first time, we demonstrate that the nosyl group can be selectively deprotected in a polymer at low potential bearing differently protected amine functional groups.

ACKNOWLEDGEMENTS

There are no conflicts to declare. The authors would like to acknowledge the financial support from the Agency for Science, Technology and Research (A*STAR) AME IRG grant (IRG17283008) - 'Microprocessor based methods of composite curing'; and Nanyang President's Graduate Scholarship provided to Nigel C. S. Tan.

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Supporting Information

Optimizing the Reduction Potential of Sulfonamides on PAMAM Dendrimers

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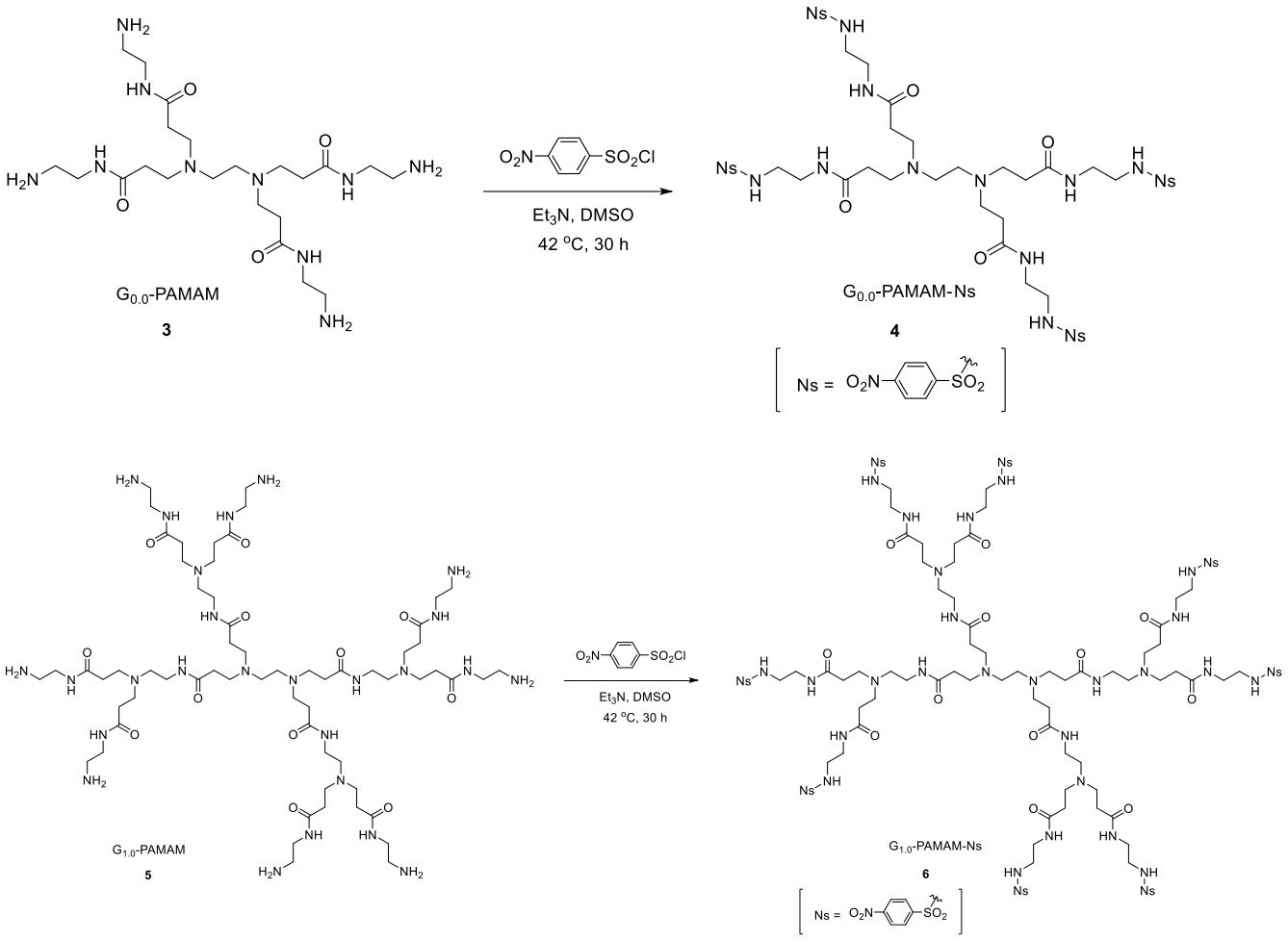
Figure S3a-b. Cyclic voltammograms of **2g** (2 mM) with AcOH (8 mM), Et_4NBr/DMF (0.1 M), and (a) naphthalene (1 mM, 2 mM), (b) pyrene (1 mM, 2 mM) using 1 mm diameter GC working electrode vs SCE at 298±2 K in a Faraday cage……[*S4*]

Figure S4. Bar chart of cathodic potentials of **2a** (2 mM) with anthracene/naphthalene/ pyrene (1 mM), Et_4NBr/DMF (0.1 M), and AcOH (8 mM) using 1 mm diameter GC working electrode vs SCE at 298±2 K in a Faraday cage. Scan rate – 0.1 V s-1……[*S5*]



Scheme S1. Synthesis of $G_{0.0}$-PAMAM-Ns and $G_{1.0}$-PAMAM-Ns.

Reagents and Conditions: (a) *p*-$NO_2C_6H_4SO_2Cl$, Et_3N, DMSO, 42 °C 30 h. 61-65%.

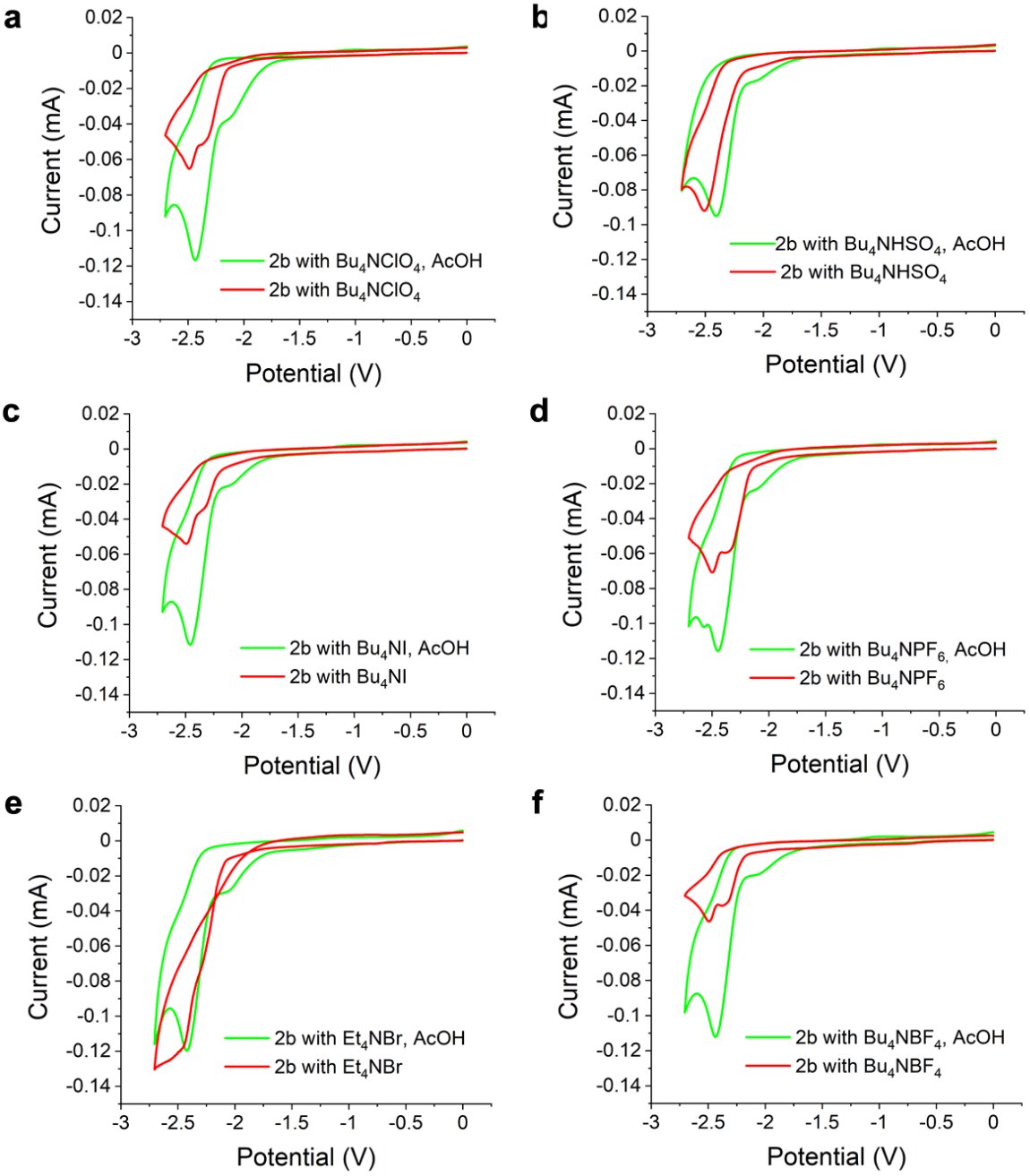


Figure S1a-f. Cyclic voltammograms of **2b** (2 mM) with and without AcOH (8 mM) and (a) Bu_4NClO_4/DMF (0.1M), (b) Bu_4NHSO_4/DMF (0.1M), (c) Bu_4NI/DMF (0.1M), (d) Bu_4NPF_6/DMF (0.1M), (e) Et_4NBr/DMF (0.1M), and (f) Bu_4NBF_4/DMF (0.1M) using 3 mm diameter GC working electrode vs SCE at 298±2 K in a Faraday cage. Scan rate – 0.1 V s^{-1}.

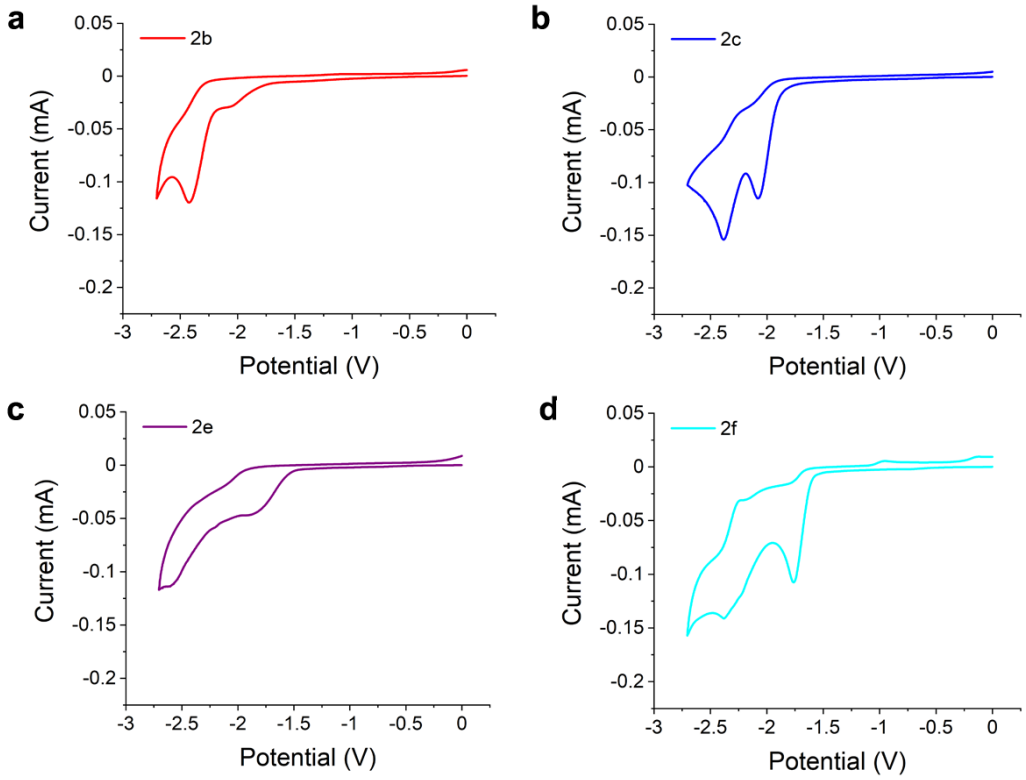


Figure S2. Cyclic voltammograms of **2b, 2c, 2e** and **2f** (2 mM) with Et_4NBr/DMF (0.1 M) and AcOH (8 mM) using 3 mm diameter GC working electrode vs SCE at 298±2 K in a Faraday cage. Scan rate – 0.1 V s^{-1}.

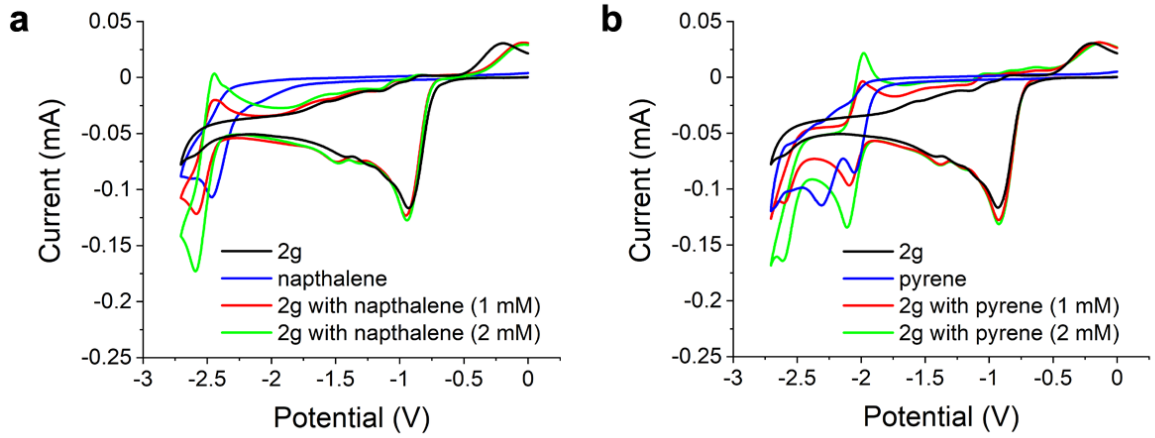


Figure S3a-b. Cyclic voltammograms of **2g** (2 mM) with AcOH (8 mM), Et_4NBr/DMF (0.1 M), and (a) naphthalene (1 mM, 2 mM), (b) pyrene (1 mM, 2 mM) using 3 mm diameter GC working electrode vs SCE at 298±2 K in a Faraday cage.

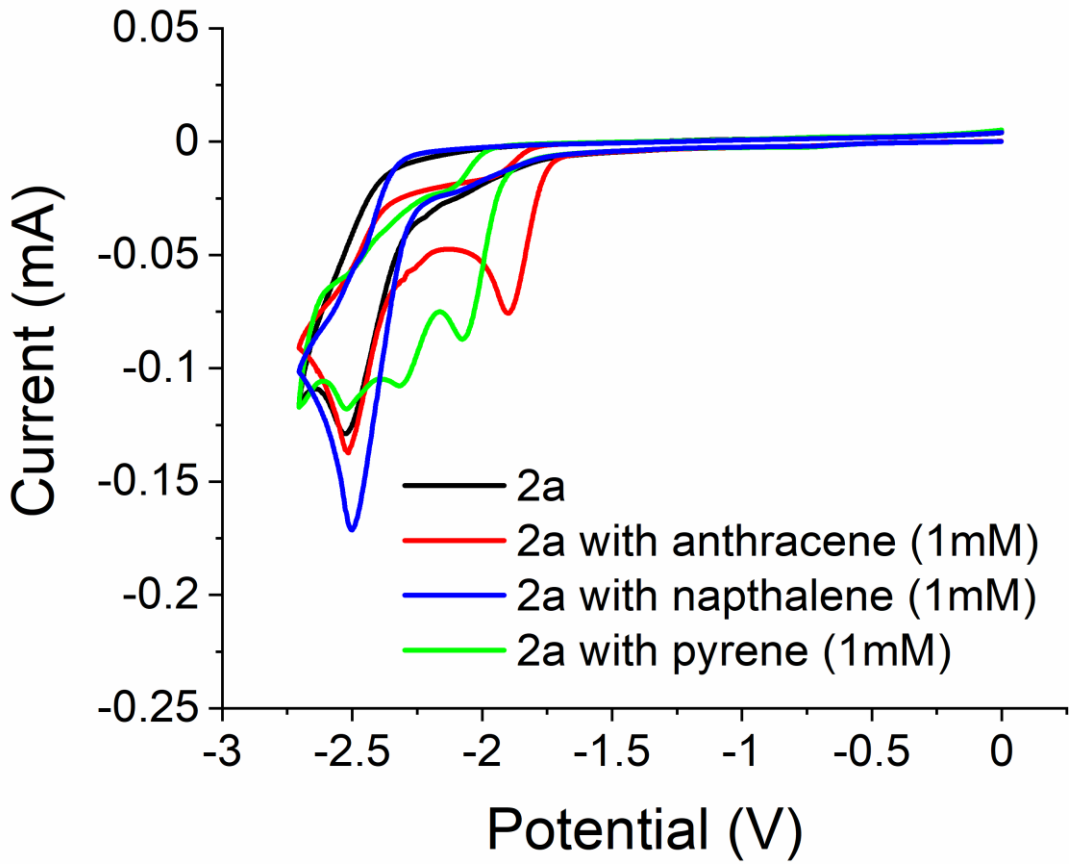


Figure S4. Cyclic voltammograms of **2a** (2 mM) with anthracene/naphthalene/ pyrene (1 mM), Et_4NBr/DMF (0.1 M), and AcOH (8 mM) using 3 mm diameter GC working electrode vs SCE at 298±2 K in a Faraday cage. Scan rate – 0.1 V s-1.