

“Janus” Calixarenes: Double-Sided Molecular Linkers for Facile, Multianchor Point, Multifunctional, Surface Modification

James P. Buttress,[†] David P. Day,[†] James M. Courtney,[†] Elliot J. Lawrence,[†] David L. Hughes,[†] Robin J. Blagg,[†] Alison Crossley,[‡] Susan E. Matthews,[§] Carl Redshaw,^{||} Philip C. Bulman Page,^{*,†} and Gregory G. Wildgoose^{*,†}

[†]School of Chemistry, University of East Anglia, Norwich Research Park, Norwich NR4 7TJ, United Kingdom

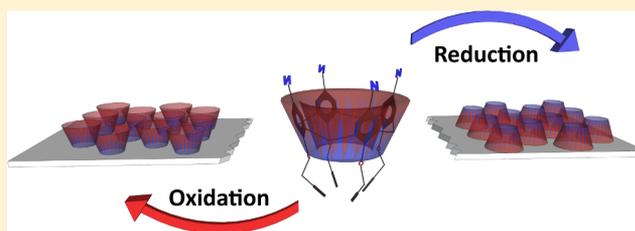
[‡]Oxford University Begbroke Science Park, Begbroke Hill, Oxford, OX5 1PF, United Kingdom

[§]School of Pharmacy, University of East Anglia, Norwich Research Park, Norwich NR4 7TJ, United Kingdom

^{||}Department of Chemistry, University of Hull, Cottingham Road, Hull, HU6 7RX, United Kingdom

Supporting Information

ABSTRACT: We herein report the synthesis of novel “Janus” calix[4]arenes bearing four “molecular tethering” functional groups on either the upper or lower rims of the calixarene. These enable facile multipoint covalent attachment to electrode surfaces with monolayer coverage. The other rim of the calixarenes bear either four azide or four ethynyl functional groups, which are easily modified by the copper(I)-catalyzed azide–alkyne cycloaddition reaction (CuAAC), either pre- or postsurface modification, enabling these conical, nanocavity reactor sites to be decorated with a wide range of substrates to impart desired chemical properties. Redox active species decorating the peripheral rim are shown to be electrically connected by the calixarene to the electrode surface in either “up” or “down” orientations of the calixarene.



INTRODUCTION

Heterogeneous support of surface-immobilized species can provide several advantages over homogeneous systems, such as being reusable, nonleaching, and nonintrusive to the systems they are employed within. When the heterogeneous support is an electrode, such systems have found myriad applications from medicinal devices¹ and flow reactors² to sensors.^{3–5} To date, the vast majority of surface immobilization strategies employ an approach of “one attachment point per modifying molecular species”. While this approach is often synthetically convenient, the disadvantage is that if the molecular attachment to the surface is broken under the reaction and/or electrolysis conditions, then the modifying species may leach from the surface, a common problem encountered in this research area. Leaching of the modifier from heterogeneous supports risks reducing lifetime and catalytic efficiency of the system or contaminating the reaction solution/product mixture. Obviously devising multipoint attachment strategies and incorporating these into the synthesis of every individual molecule that one might wish to support on a surface would be both laborious and impractical. Instead, we have devised a generic macromolecular scaffold using modified calix[4]arenes that serve as double-sided, conductive, molecular “sticky tape”, which are facile to produce in gram quantities. Either the top or bottom of the calixarene may be used to form four-point attachments to a surface while the other side is decorated with up to four

modifying species.⁶ We have dubbed these “Janus” calixarenes after the two-faced Roman god.

Calix[4]arenes are multifunctionalizable macromolecules made up of four aromatic subunits connected by methylene linkers.⁷ With suitable functional groups in place, calix[4]arenes can be locked into a cone-shaped geometry, which, like the Greek vase (“calix”) they are named after, have a wider upper rim and a narrower lower rim enclosing a hydrophobic, nanometer-sized, central cavity (Figure 1). Typically calixarenes are modified at two positions on the aromatic rings: the lower rim positions, which are commonly decorated with phenolic or ether groups, and the carbon atoms *para* to these positions that form the upper rim. The structural modification of calixarenes is an extensive area of research that has been reviewed by several authors in recent years,^{8,9} with reports of upper-rim functionalization ranging from the use of biomolecular species such as peptides for the binding of small molecules and ligands,¹⁰ urea-modified calix[4]arenes that participate in host–guest interactions with target substrates,¹¹ through to organometallic catalysts for polymerization reactions.¹² Modification of the lower rim of the calixarene structure, while less commonly reported, has been shown to enable calix[4]arenes to act as fluorescent reagents for sensing various anions and

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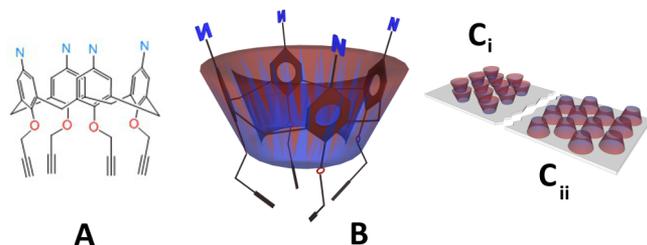


Figure 1. (A) Structure of Janus calix[4]arene (“N” groups are either azide or amine functionality). (B) Illustrates the cone structure of Janus calixarene. (C) The calixarene immobilized onto a surface by (i) the lower rim and (ii) the upper rim.

fications.¹³ Furthermore, due to their unique 3D conical structure, calix[4]arenes have been shown to form densely packed monolayers on surfaces,¹⁴ a property that we wish to exploit.

Previous strategies to attach large macrocyclic substrates such as calixarenes,¹⁵ resorcinarenes,¹⁶ and cyclodextrins¹⁷ to surfaces have predominantly focused on the spontaneous adsorption of their thiol derivatives onto gold. This highly adaptable method is effective for a large array of substrates. However, this approach suffers one important limitation: the relatively weak gold–thiol bond is prone to cleavage resulting in a lack of thermal stability^{18,19} and a relatively narrow electrochemical window in which to operate.²⁰ Furthermore, this attachment strategy is only effective on “coinage” metals such as platinum, nickel, and gold. In order to make our Janus calixarene approach universally applicable to the modification of both metallic and nonmetallic (e.g., ubiquitous and inexpensive graphitic supports/electrode surfaces) we have chosen two alternative strategies: (i) the reduction of aryl diazonium functionalities incorporated into the calix[4]arenes; (ii) the oxidation of lithio-activated alkyne moieties on the calix[4]arene. Either strategy is applicable to the modification of a range of metallic and nonmetallic surfaces^{21–23} and can be selected to complement any redox sensitivity of the target modifying species when attached to the Janus calixarene prior to surface attachment.

The electrochemical one-electron reduction of aryl diazonium salts (generating a reactive aryl radical intermediate with loss of N₂) was first reported by Pinson et al.²⁴ in 1992 and has gained significant interest since then.^{25,26} It is a highly versatile method of immobilizing compounds to solid supports, as aryl diazonium salts are easily generated from the corresponding aniline derivatives in either aqueous or nonaqueous solvents. Similarly, the electrografting process can take place in either aqueous²⁷ or organic media²⁸ and involves the formation of strong, robust C–C or C–metal bonds. Bulk surface modification is also readily achievable by chemical, rather than electrochemical, reduction of the diazonium salts, for example, by using hypophosphorous acid.²⁹ The only minor drawback of this approach is that simple precautions must be taken to avoid the formation of disorganized, multilayer, films.^{30,31}

The alternative surface attachment protocol we have selected, involving the oxidation of lithio-activated alkynes, was first described by Geiger et al. in 2013.³² They initially demonstrated that several reactive organometallic complexes bearing pendent propargyl groups (–CH₂C≡CH) could be electrografted onto carbon and precious metal electrodes; in

later work, Geiger’s group has extended this methodology to porphyrins.³³ The one-electron oxidation of either a terminal alkyne or lithio-alkyne results in the rapid loss of H⁺ or Li⁺, respectively, to form the desired propargyl radical intermediate for bond formation to the electrode surface.³³ Herein, we demonstrate that this approach can also be extended to covalently attach calixarenes to electrode surfaces.

Having selected two complementary and widely applicable surface attachment strategies, we were only left with the question of how to attach the target modifying molecules to the calixarene in a way that is applicable for a wide a range of different substrates. To this end, we report methods to functionalize either the upper or lower rim of calix[4]arenes, the rim not used for attachment to the surface with either azide or ethynyl moieties. Simple incorporation of alkyne or azide groups onto the target substrate allows us to couple the substrate to the calixarene tethers using the extremely versatile copper(I) catalyzed alkyne–azide cycloaddition (CuAAC) reaction.³⁴ The substrate is then bound to the calixarene via a chemically and electrochemically robust triazole linkage.^{35,36} Furthermore, we show that full modification of each Janus calixarene with four modifying species can be accomplished using the CuAAC approach either before or, crucially, after the surface modification step.

Given the enormous scope of substrates that are amenable to this approach, in this report we are focused on presenting the synthesis, characterization, and multipoint, robust, electrode surface modification of four different Janus calixarenes attached to the surface using two different strategies and each bearing four identical functional groups on either upper or lower rims comprising of (i) organic nitro functionalities; (ii) organo-metallic azide-functionalized ferrocenyl moieties; (iii) ethynyl-functionalized ferrocenyl groups; (iv) organic 1-ethynyl-3,5-bis(trifluoromethyl)benzene moieties. Substrates (i–iii) are used to demonstrate that the aromatic and unsaturated Janus calixarene linkers enable electron transfer to redox active centers attached at either the upper or lower rim of the calixarene. Substrate (iv) is used as an XPS label to aid in surface characterization and to demonstrate that full functionalization of the Janus calixarenes can be readily achieved through CuAAC reactions after surface attachment of the calixarene. Aside from presenting synthetic routes to novel functionalized calix[4]arenes, including the first examples of tetraazido (upper rim) functionalized calix[4]arenes, this report seeks to demonstrate widespread applicability in providing a facile method of covalently attaching more than one species through more than one bond to a surface proffered by the use of Janus calixarenes.

RESULTS AND DISCUSSION

Suitable calix[4]arenes were synthesized for attachment to a glassy carbon electrode (GCE) surface at either the upper or lower rim. Once bound to the GCE surface, the exposed face of the calixarene was designed for facile modification using the copper-catalyzed azide alkyne cycloaddition (CuAAC) reaction.

Our starting material, *p*-*tert*-butylcalix[4]arene **1**, was *O*-alkylated with four propargyl groups following Chetcuti’s procedure.³⁷ Attaching groups to the lower rim ensures that the calix[4]arenes maintain a cone confirmation (confirmed by the presence of two characteristic doublets in the ¹H NMR spectra of every calix[4]arene studied, each corresponding to 4 methylene protons in the region of ca. 2.7–4.6 ppm)³⁸ throughout the synthesis. The *ipso*-nitration to functionalize the

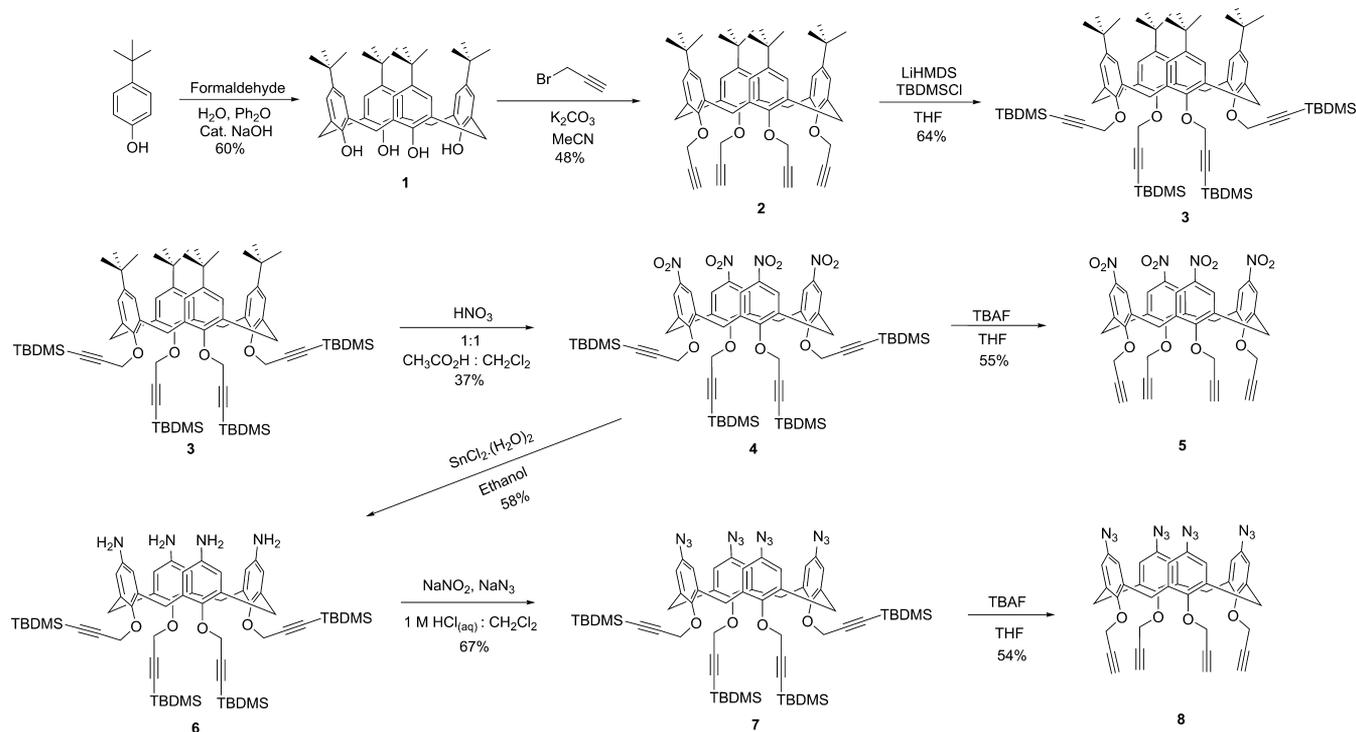


Figure 2. Synthesis of cone-5,11,17,23-tetra-azido-25,26,27,28-propargylcalix[4]arene **8**.

upper rim of the calixarene was conducted using fuming nitric acid and glacial acetic acid.³⁹ However, attempting the nitration reaction without first protecting the reactive terminal alkyne substituents failed to yield any of the desired product. Therefore, the propargyl groups were protected using *tert*-butyldimethylsilyl (TBDMS) groups, whereupon the nitration of the upper rim proceeded smoothly, leaving the alkyne groups intact. The nitro functionalities were then reduced using $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ ⁴⁰ in refluxing ethanol to afford the novel cone-5,11,17,23-tetra-amino-25,26,27,28-TBDMS-propargylcalix[4]arene **6**. Employing the Sandmeyer reaction, **6** was converted into compound **7**, through formation of the corresponding tetradiazonium salt by using sodium nitrite in dilute hydrochloric acid and subsequently performing a nucleophilic aromatic substitution with sodium azide. Removal of the TBDMS protecting groups using a solution of 1 M *t*-butylammonium fluoride (TBAF) in THF afforded target molecule **8** (see Figure 2). TBAF was also used to remove the TBDMS groups of molecule **4** to give the unprotected 5,11,17,23-tetra-nitro-25,26,27,28-propargylcalix[4]arene **5**. This novel calix[4]arene is highly versatile with either rim being easily modifiable by the CuAAC reaction, affording us a very stable and functionalizable scaffold surrounding a hydrophobic cavity.

All novel compounds were fully characterized by mass spectrometry, nuclear magnetic resonance (NMR), and IR spectroscopy (see Supporting Information for more information). Only the final products require purification by flash chromatography before being attached to the electrode surface.

Attachment of Janus Calixarenes by the Upper Rim. The surface of a GCE was modified with tetraaminocalix[4]arene **6** to form a robust, versatile platform that can be functionalized by a large array of substrates using the CuAAC reaction. The immobilization of calix[4]arene **6** was performed by the formation of its tetradiazonium salt, by reaction of **6** with

stoichiometric sodium nitrite in 1 M hydrochloric acid. The diazonium salt was then reduced onto the electrode surface either *in situ*⁴¹ or by isolating the salt and performing the reduction in anhydrous acetonitrile using $[\text{nBu}_4\text{N}][\text{PF}_6]$ as electrolyte.⁴² During the first reductive scan, we observed a broad irreversible reduction at -0.35 V versus Ag/Ag^+ , corresponding to the one-electron reduction of the diazonium salt to the phenyl radical, which then bonds to the electrode surface. Subsequent scans exhibited a large decrease in the background capacitance, suggesting that the exposed rim of the calixarene, modified with large silyl protecting groups, acts as a blocking layer to the electrode, passivating the surface (see Supporting Information Figure S45). The passivation observed is consistent with the electrografting of similar molecules in the literature.³⁰

Having electro-reduced the diazonium salt onto the GCE surface, further functionalization was conducted using the CuAAC reaction.⁴³ The alkyne was deprotected using 1 M TBAF, and ferrocenyl methyl azide was added to the immobilized calixarenes in a “click” reaction generating a triazole linker. This produced a ferrocene-modified calixarene on the surface of the GCE, as shown in Figure 3A. In principle, this method can be adapted for a large array of substrates. Models of all immobilized and postsurface-modified calix[4]arenes were also separately synthesized in solution and fully characterized to show that they are indeed formed under these conditions and that they maintain their cone conformations (see Supporting Information, molecules **10** and **13**).

After attaching the ferrocene moieties by the CuAAC reaction, the electrode was thoroughly rinsed to remove any physisorbed material (see Supporting Information). The GCE was transferred to a fresh anhydrous electrochemical cell containing 0.1 M $[\text{nBu}_4\text{N}][\text{PF}_6]$ in 10 mL dichloromethane. A well-defined reversible oxidation of the ferrocene moiety was observed, centered at 0.16 V versus $\text{Cp}_2\text{Fe}^{0/+}$, as illustrated in

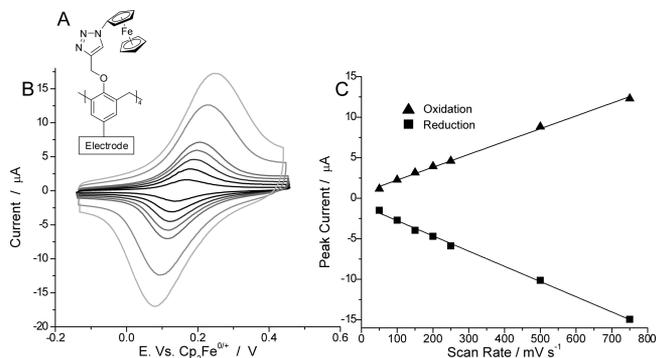


Figure 3. (A) Calix[4]arene 13 immobilized onto GCE surface. (B) Overlaid cyclic voltammograms recorded in $\text{CH}_2\text{Cl}_2/0.1 \text{ M } [\text{nBu}_4\text{N}][\text{PF}_6]$ at scan rates of 50–750 mV s^{-1} for a GC electrode modified with calixarene 6 after further modification with ferrocenyl methyl azide moieties to form calix[4]arene 13 attached by the upper rim. (C) Corresponding plot of peak current versus scan rate.

Figure 3B. It was noted that the peak current corresponding to the reversible oxidation increases linearly upon increasing the voltage scan rate from 50–750 mV s^{-1} , as shown in **Figure 3C**. This result is clearly indicative of a surface-bound redox active species. In contrast, a redox active species in solution would exhibit a mass-transport limited diffusional response typified by a linear dependence of peak current upon the square root of the voltage scan rate. It is also important that over multiple scans the current corresponding to the ferrocene redox couple did not decrease, suggesting the surface adsorbed species is electrochemically stable.

The surface concentration, Γ (mol cm^{-2}) of ferrocene attached to the GCE surface was calculated from the peak areas. Assuming complete coupling of the ferrocenyl moieties to every available site on the calixarene, the surface coverage of ferrocene-modified calixarene was found to be $\Gamma = 1.3 \times 10^{-10} \text{ mol cm}^{-2}$. Note that this assumption sets a lower limit on the calculated surface coverage of the calixarene linkers. Nevertheless, this value indicates a packing density of immobilized calixarenes on the surface of 0.78 calix nm^{-2} . This compares very favorably with the theoretical maximum value for a hexagonally packed monolayer of calixarenes (modeled as discs of diameter 11.6 Å derived from crystallographic dimensions of structurally similar calixarenes) of 0.85 calix nm^{-2} ,⁴⁴ strongly supporting the formation of a complete monolayer of surface immobilized calixarene linkers on the electrode surface. After formation of the monolayer, we were able to functionalize the adsorbed calixarenes with different organic and organometallic substrates using the CuAAC reaction. These calixarenes serve as excellent molecular tethers, connecting the redox active moieties to the electrode surface, while ensuring good electron conductivity between ferrocenyl units and the electrode, and effectively blocking the electrode surface to other redox active species that may be in solution.

Attachment of Janus Calixarenes by the Lower Rim.

Attachment of calix[4]arenes 5 and 8 at the lower rim to a GCE surface was achieved using the pendent propargyl ether groups. The formation of ethynyl-based radicals, generated by anodic oxidation of “lithio-activated” terminal ethynyl groups³² was used to electrochemically graft the substrates onto the surface. Lithiation of each calix[4]arene 5 or 8 was conducted in an anhydrous electrochemical cell containing a 0.1 M solution of $[\text{nBu}_4\text{N}][\text{PF}_6]$ and 4 mM calixarene dissolved in 10 mL of THF

cooled to -78°C . Dilute (1.6 M) *n*-BuLi was added slowly to the reaction mixture and stirred for 20 min. Cyclic voltammetric characterization of the solutions revealed a large irreversible anodic oxidation wave present at 0.6 V versus Ag/Ag^+ for both calix[4]arenes 5 and 8 (see **Supporting Information** Figure S46), corresponding to the irreversible, one-electron oxidation of lithio-ethynyl groups on each calixarene.³² Next, a chronoamperometric experiment was performed by holding the potential of the working electrode beyond the onset of oxidation, 0.9 V versus Ag/Ag^+ for 300 s to electrograft substrates 5 and 8 separately onto different electrode surfaces. Note if the electrografting is attempted without the addition of *n*-BuLi, no oxidation is observed, suggesting that activation of the alkyne groups is essential to facilitate attachment onto the GCE.

With calixarene 5 bound to the GCE, the electrode was thoroughly rinsed to remove any physisorbed species and placed into an aqueous electrochemical cell containing 10 mL of 1 M hydrochloric acid and 1.0 M KCl. The cyclic voltammetry obtained from this system showed a large irreversible reduction on the first scan at -0.52 V versus SCE (peak 1 in **Figure 4A**), which corresponds to the chemically and

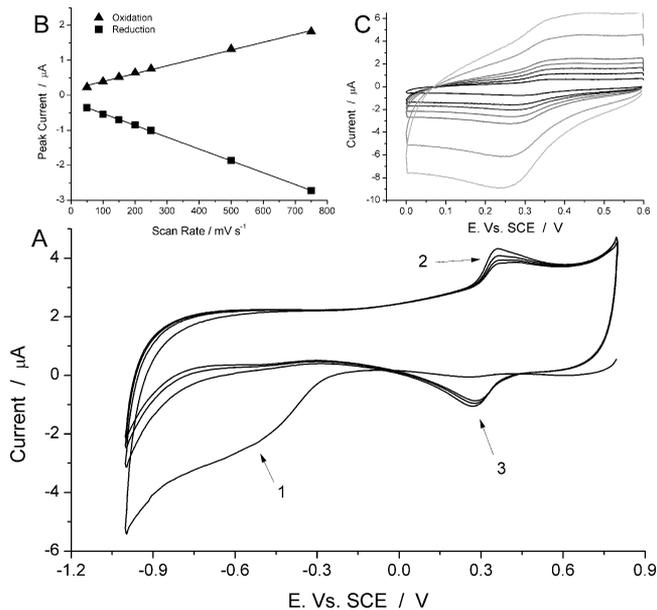


Figure 4. (A) Overlaid cyclic voltammograms of a GC electrode modified with 5 in 1 M HCl/1 M KCl, scan rate 0.1 V s^{-1} . (B) Corresponding plot of peak current versus scan rate. (C) Overlaid cyclic voltammograms of the modified electrode recorded at 50–750 mV s^{-1} over the reversible arylhydroxylamine/arylnitroso redox couple.

electrochemically irreversible four-electron, four-proton reduction of the nitro functional groups on the calix[4]arene. After sweeping to potentials beyond this initial reduction and then reversing the scan direction a new oxidation wave was observed (peak 2). On further cycling, a new reduction peak (peak 3) was observed corresponding to peak 2; reduction peak 1 was no longer observed. This new, chemically and electrochemically reversible system (peaks 2 and 3), centered at 0.33 V versus SCE, corresponds to the two-electron, two-proton arylhydroxylamine/arylnitroso redox couple. The observed voltammetric behavior is characteristic of the redox chemistry of aryl nitro groups, and confirms the presence of calix[4]arene 5 on the

electrode surface. Next, the voltage scan rate was varied between 50 and 750 mV s⁻¹ over the quasi-reversible arylhydroxylamine/arylnitroso region (Figure 4B). Once again, the oxidative and reductive peak currents were found to increase linearly with respect to the voltage scan rate (Figure 4C), confirming that the calix[4]arene **5** is indeed bound to the electrode surface.

The GCE modified with tetraazidocalix[4]arene **8** was treated with ethynyl ferrocene in the presence of Cu(I) to afford a ferrocenyl-modified calixarene immobilized onto the electrode surface shown in Figure 5C. The electrode was

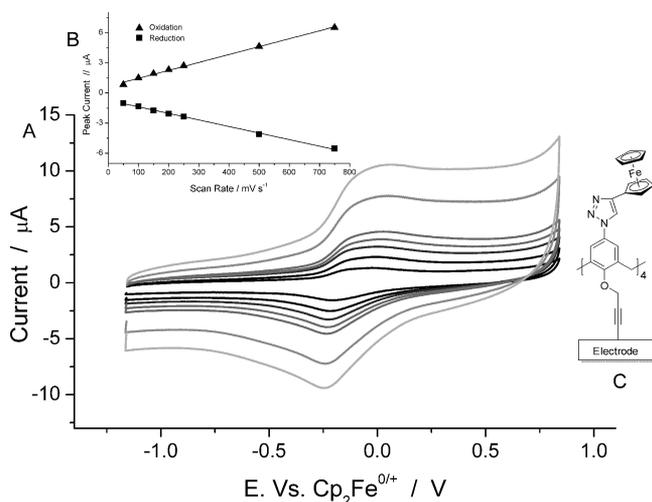


Figure 5. (A) Overlaid cyclic voltammograms of a GCE modified with **8** after postsurface modification in CH₂Cl₂/0.1 M NBu₄PF₆, scan rate 0.05–0.75 mV s⁻¹. (B) Corresponding plot of peak current versus scan rate. (C) Structure of modified electrode surface.

thoroughly rinsed and transferred to an electrochemical cell containing 0.1 M [ⁿBu₄N][PF₆] in dry dichloromethane. Cyclic voltammetry was conducted at scan rates ranging from 50 to 750 mVs⁻¹ (Figure 5A). We observed a nonideal reversible oxidation of the ferrocenyl moiety centered at -0.27 versus Cp₂Fe^{0/+}, where the peak current was again linearly dependent on the voltage scan rate, again indicative of a surface bound redox species (Figure 5B). Note, the wave-shape of the redox couple of the ferrocene moieties is nonideal, presumably, caused by the requirement for electrons to hop over the propargyl-ether linkers and/or the lateral interactions between charged centers around the upper rim. Whereas, the sharp reductive signal is attributed to the release of counterions from the oxidized electrode surface, during the reduction process. Furthermore, it is important that the peak current remained constant over numerous scans suggesting that the chemisorbed material remains anchored to the electrode surface.

The surface concentration Γ (mol cm⁻²) of the ferrocene groups attached to the GCE surface was calculated from the oxidative and reductive peak areas to be $\Gamma = 5.6 \times 10^{-10}$ mol cm⁻². Assuming conversion of all the azide functional groups into the triazole-linked ferrocene moieties, this corresponds to a surface coverage of 0.84 calix nm⁻². Again, this value compares favorably with the theoretical value of 0.90 calix nm⁻² for a hexagonally packed monolayer of calix[4]arenes (assumed to be discs of diameter 11.3 Å, derived from the crystallographically determined dimensions of **5**), indicating that we are able to attach a complete monolayer of calixarene linkers

covalently to a GCE. Furthermore, this linker is shown to be easily functionalized on the GCE surface at all four sites on the upper rim using the CuAAC reaction.

XPS studies were also used to analyze the attachment and postsurface modifications of the calixarene linkers. This was conducted using a clean GCE that was modified with calixarene **8** using the lithiation and electrografting methodology described above. Instead of using a redox active probe we modified the immobilized calix[4]arene **8** molecular tether with 1-ethynyl-3,5-bis(trifluoromethyl)benzene, following the CuAAC reaction protocol as described in the Supporting Information. This introduces a fluorine-labeled probe onto the surface, whose presence is easily identified by X-ray photoelectron spectroscopy. The modified GCE was then thoroughly rinsed in a variety of solvents to remove any physisorbed species and analyzed using XPS. The full survey spectrum (see Supporting Information Figure S47) shows characteristic F_{1s} and N_{1s} signals from the probe molecules in addition to C_{1s} and O_{1s} signals arising from the GC surface. We also observed a small amount of Cl_{2p} and Si_{2p} impurities introduced by the polishing steps used to clean the electrode surface.

Strong evidence for the successful modification of the calixarenes after their surface immobilization onto the GCE is given by the presence of the peaks observed at binding energies of 399.7 and 688.3 eV (Figure 6). These correspond to the N_{1s}

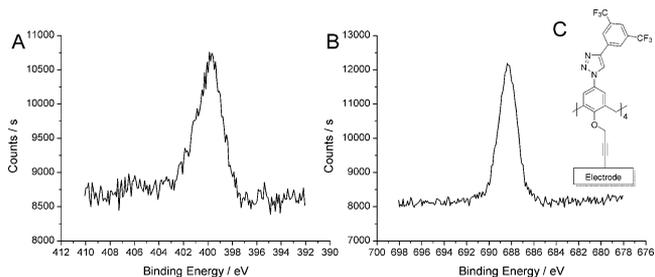


Figure 6. XPS spectra recorded over (a) the N_{1s} region and (b) the F_{1s} region of the modified GCE. (c) Structure of the functionalized calixarene attached to the GCE surface.

signal from the three nitrogen atoms in each of the triazole rings and the F_{1s} signal arising from the six fluorine atoms in the CF₃ groups of the 3,5-(trifluoromethyl)benzene moieties, respectively. Note that had any unreacted azide groups been present on the GCE surface, these would have given rise to two characteristic nitrogen signals at 405 and 401 eV in a ratio of 1:2,⁴⁵ which are not observed. Figure 6A shows that we observe only one distinct triazole N_{1s} signal, suggesting that we have achieved complete modification of the calixarene molecular tether at almost all available reactive sites using the CuAAC reaction.

Further evidence in support of this claim is found in the ratio between the observed N_{1s} and F_{1s} signals measured in the XPS spectrum. After adjusting for the relative atomic sensitivity factors,^{46,47} the relative abundance of the two elements on the surface of the GCE was found to be 1:1.9 (nitrogen/fluorine). This is very close to the 1:2 ratio of nitrogen/fluorine expected for complete modification of the surface-bound calixarene with 1-ethynyl-3,5-bis(trifluoromethyl)benzene moieties. Furthermore, the “click” reaction was performed on calix[4]arene **7** under similar conditions in solution to show that the molecule can be readily synthesized and maintains its cone confirmation (see Supporting Information Molecule 9).

EXPERIMENTAL SECTION

Commercially available reagents were purchased from Sigma-Aldrich (Gillingham, U.K.) and used without further purification unless stated otherwise. Anhydrous reactions were performed under a dry nitrogen atmosphere (BOC Gasses) using standard Schlenk-line techniques on a dual manifold vacuum/inert gas line. All glassware was dried in the oven overnight before use. Anhydrous solvents were dried via distillation over either sodium/benzophenone (tetrahydrofuran (THF) and diethyl ether) or calcium hydride (dichloromethane (DCM)) under an inert nitrogen atmosphere and sparged with nitrogen gas to remove any trace amounts of dissolved oxygen. Water used in aqueous electrochemical reactions was also thoroughly sparged with nitrogen to remove dissolved oxygen prior to use. After any surface modification, the electrode was sonicated for 10 min in each of the following solvents, water, acetone, and dichloromethane, before being allowed to dry.

Electrochemical measurements were performed under an inert atmosphere using computer-controlled potentiostat (Model PGSTAT 30, Autolab, Utrecht, The Netherlands) using a standard three-electrode configuration: a glassy carbon electrode (GCE) (BasiTechnical, diameter 3 mm) served as the working-electrode with a platinum wire counter electrode (99.99%, GoodFellow, Cambridge, U.K.) and either a silver wire pseudoreference electrode (99.99%, GoodFellow, Cambridge, U.K.) or a saturated calomel electrode (Radiometer, Copenhagen, Denmark) used as the reference electrode for non-aqueous and aqueous electrochemical measurements, respectively. The working electrode surface was renewed by successive polishing with diamond paste slurries of decreasing particle size ranging from 3.0 to 0.1 μm (Kemmet, U.K.). The electrode was sonicated in deionized water and rinsed with ethanol between each polishing step to remove any adhered polishing materials.

Flash chromatography was performed on silica gel (SiO_2 , 70–200 μm mesh 60 Å) purchased from Alfa Aesar. Thin layer chromatography was performed using silica gel 60 Å F254 pre-coated plates.

Proton NMR (^1H NMR) spectra were recorded using a Bruker Avance DPX-500 MHz spectrometer. The data is reported as s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad; coupling constant(s) in Hz. Chemical shifts are reported in parts per million (ppm) relative to CDCl_3 (7.26 ppm). Carbon NMR (^{13}C NMR) spectra were recorded at 75 and 125 MHz. Chemical shift is reported in ppm relative to the carbon resonance of CDCl_3 (77.00 ppm). IR spectra were recorded using a PerkinElmer μ -ATR Spectrum II spectrometer. X-ray photoelectron spectroscopy (XPS) was performed with a Thermo Scientific K-alpha instrument using monochromatic Al X-rays. All spectra were corrected relative to the graphitic C_{1s} peak position (284.97 eV). Calix[4]arenes **1**^{48,49} and **2**³⁷ where synthesized following modified literature procedures full details in Supporting Information.

Synthesis of cone-5,11,17,23-Tetra-tert-butyl-25,26,27,28-TBDMS-propargylcalix[4]arene 3. To a 3-necked 100 mL round-bottom flask, *tert*-butyldimethylsilyl chloride (14.7 g, 97.5 mmol) was dissolved in anhydrous THF (50 mL). In a separate flask, **2** (12 g, 16.2 mmol) was added and dissolved in anhydrous THF (100 mL); this was then cooled to -78°C , and over a period of 15 min lithium bis(trimethylsilyl)amide solution (1.0 M in THF, 100 mL, 97.5 mmol) was added, resulting in a dark brown reaction mixture. After 30 min the flask containing *tert*-butyldimethylsilyl chloride in THF was added dropwise, via cannula to the solution containing the deprotonated calixarene, **2**. After complete addition, the flask was allowed to warm to room temperature overnight. The reaction was then quenched by the addition of a saturated solution of ammonium chloride (100 mL). The organic layer was separated, and the aqueous layer was washed with dichloromethane (100 mL). The organic extracts were combined and dried over MgSO_4 , and the remaining solvents removed in vacuo. The product **3** was isolated as a light brown solid (12.0 g, 64%). ^1H NMR (500 MHz, CDCl_3 , δ): 0.09 (24H, s), 0.90 (36H, s), 1.06 (36 H, s), 3.12 (4H, d, $J = 13$ Hz), 4.52 (4H, d, $J = 13$ Hz), 4.83 (8H, s), 6.75 (8H, s). ^{13}C NMR (125 MHz, CDCl_3 , δ): -4.5 , 16.6, 26.3, 31.5, 32.7, 34.0, 61.4, 89.5, 103.6, 124.9, 134.8, 145.3, 152.1. IR (neat, ν/cm^{-1}):

2952, 2929, 2855, 2167 (alkyne), 1739, 1480, 1361, 1248, 1196, 1120, 1040. HRMS: m/z : $[\text{M} + \text{NH}_4]^+$ calcd for $\text{C}_{80}\text{H}_{120}\text{O}_4\text{Si}_4$, 1274.8607; found, 1274.8581

Synthesis of cone-5,11,17,23-Tetra-nitro-25,26,27,28-TBDMS-propargylcalix[4]arene 4. To a round-bottom flask cooled to 0°C was added **3** (13 g, 10.4 mmol) dissolved in dichloromethane (130 mL) and glacial acetic acid (130 mL). Using a glass syringe, 100% nitric acid (54 mL, 1.29 mol) was added dropwise at 0°C . After complete addition, the flask was allowed to warm to room temperature overnight. The reaction was then poured into iced water (200 mL), and the organic layer was separated by extraction. The aqueous layer was washed with dichloromethane (3×50 mL); the remaining organic phases were combined and dried with MgSO_4 , and the remaining solvents were evaporated in vacuo. Redissolving the resulting residue in dichloromethane, followed by trituration with methanol yielded **4** as a cream powder (4.6 g, 37%). ^1H NMR (500 MHz, CDCl_3 , δ): 0.08 (24H, s), 0.86 (36H, s), 3.44 (4H, d, $J = 14$ Hz), 4.66 (4H, d, $J = 14$ Hz), 4.91 (8H, s), 7.71 (8H, s). ^{13}C NMR (125 MHz, CDCl_3 , δ): -4.7 , 16.5, 26.0, 32.3, 62.6, 93.4, 99.9, 124.2, 136.3, 144.0, 159.7. IR (neat, ν/cm^{-1}): 2952, 2885, 2857, 2929, 2179 (alkyne), 1738, 1714, 1587, 1524 (nitro asymmetric), 1462, 1345 (nitro symmetric), 1251, 1205, 1096. HRMS: m/z : $[\text{M} + \text{NH}_4]^+$ calcd for $\text{C}_{80}\text{H}_{120}\text{O}_4\text{Si}_4$, 1230.5501; found, 1230.5497.

Synthesis of cone-5,11,17,23-Tetra-nitro-25,26,27,28-propargylcalix[4]arene 5. Calixarene **4** (1 g, 0.82 mmol) was dissolved in a 1 M solution of tetra-*n*-butylammonium fluoride (TBAF) in THF (16.5 mL, 16.5 mmol) at room temperature and the reaction was monitored by TLC. Once complete, the reaction was quenched by the addition of cold water (100 mL), and the product was extracted with dichloromethane (3×50 mL) washings of the aqueous layer. The combined organic layers were then washed with water (2×100 mL) and dried using MgSO_4 . The filtrate was concentrated in vacuo, and the residue was purified using flash chromatography (acetone/petroleum ether 1:4) to afford **5** as a pale yellow-orange solid (0.34 g, 55%). ^1H NMR (500 MHz, CDCl_3 , δ): 2.60 (4H, t, $J = 2$ Hz), 3.49 (4H, d, $J = 14$ Hz), 4.72 (4H, d, $J = 14$ Hz), 4.86 (8H, d, $J = 2$ Hz), 7.71 (8H, s). ^{13}C NMR (125 MHz, CDCl_3 , δ): 26.0, 62.6, 93.4, 99.9, 124.2, 136.3, 144.0, 159.7. IR (neat, ν/cm^{-1}): 3287, 3079, 2931, 2120 (alkyne), 1704, 1585, 1519 (nitro asymmetric), 1459, 1342 (nitro symmetric), 1202, 1093. HRMS: m/z : $[\text{M} + \text{NH}_4]^+$ calcd for $\text{C}_{40}\text{H}_{32}\text{N}_5\text{O}_{12}$, 774.2042; found, 774.2044.

Synthesis of cone-5,11,17,23-Tetra-amino-25,26,27,28-TBDMS-propargylcalix[4]arene 6. Calix[4]arene **5** (4 g, 3.3 mmol) was dissolved in ethanol (200 mL) to which $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ (40 g, 177 mmol) was added and stirred at room temperature for 15 min. The reaction mixture was then submitted to reflux for 48 h. After allowing the reaction to cool to room temperature, 10% NaOH solution (200 mL) was added to basify the reaction mixture. Extraction of the aqueous layer with dichloromethane (3×200 mL), followed by drying of the organic extracts over MgSO_4 and solvent evaporation under reduced pressure afforded compound **6** as a light brown solid (2.05 g, 58%). ^1H NMR (500 MHz, CDCl_3 , δ): 0.08 (24H, s), 0.90 (36H, s), 2.93 (4H, d, $J = 13$ Hz), 4.45 (4H, d, $J = 13$ Hz), 4.69 (8H, s), 6.11 (8H, s). ^{13}C NMR (125 MHz, CDCl_3 , δ): -4.5 , 16.6, 26.2, 31.1 (t, $J = 167$ Hz), 61.7, 89.4, 103.7, 115.6, 136.2, 141.2, 148.2. IR (neat, ν/cm^{-1}): 3325 (amine), 2954, 2928, 2855, 2173 (alkyne), 1606 (amine), 1471, 1361, 1249, 1207, 1097. HRMS: m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{64}\text{H}_{93}\text{N}_{40}\text{O}_4\text{Si}_4$, 1093.6267; found, 1093.6269.

Synthesis of cone-5,11,17,23-Tetra-azido-25,26,27,28-TBDMS-propargylcalix[4]arene 7. To a stirred solution of **6** (1.5 g, 1.37 mmol) in trifluoroacetic acid (TFA) (10 mL) at 0°C a solution of NaN_3 (900 mg, 13 mmol) in cold water was added dropwise and the mixture was stirred at 0°C for 10 min. After this time, a solution of NaN_3 (1.8 g, 26 mmol) in cold water was added dropwise and the reaction mixture was stirred at 0°C for 45 min. Dichloromethane (10 mL) was then added and the reaction was allowed to warm up to room temperature overnight. The reaction was diluted with water and extracted with dichloromethane (3×25 mL) washings of the aqueous layer. The combined organic layers were dried over MgSO_4 , filtered and concentrated in vacuo. The residue was purified using flash

chromatography (ethyl acetate/petroleum ether 1:10) to afford 7 as pale yellow powder (1.0 g, 67%). ^1H NMR (500 MHz, CDCl_3 , δ): 0.08 (s, 24H), 0.88 (s, 36H), 3.13 (d, $J = 13.6$ Hz, 4H), 4.53 (d, $J = 13.6$ Hz, 4H), 4.73 (s, 8H), 6.37 (s, 8H). ^{13}C NMR (125 MHz, CDCl_3 , δ): -4.58, 16.53, 26.13, 61.96, 91.01, 101.97, 118.69, 134.78, 136.98, 152.12. IR (neat, ν/cm^{-1}): 2953, 2927, 2856, 2177 (alkyne), 2107 (azide), 1656, 1587, 1468, 1361, 1317, 1249, 1233, 1201, 1024. HRMS: m/z : $[\text{M} + \text{NH}_4]^+$ calcd for $\text{C}_{64}\text{H}_{88}\text{N}_{13}\text{O}_4\text{Si}_4$, 1214.6154; found, 1214.6153.

Synthesis of cone-5,11,17,23-Tetra-azido-25,26,27,28-propargylcalix[4]arene 8. Calixarene 7 (750 mg, 0.63 mmol) was dissolved in a 1 M solution of TBAF in THF (13 mL, 13 mmol) at room temperature, and the reaction was monitored by TLC. Once complete, the reaction was quenched by the addition of cold water (100 mL), and the product was extracted with dichloromethane (3×50 mL) washings of the aqueous layer. The combined organic layers were then washed with water (2×100 mL), dried using MgSO_4 . The filtrate was concentrated in vacuo, and the residue was purified using flash chromatography (acetone/petroleum 1:4) to afford 8 as a yellow solid (0.25 g, 54%). ^1H NMR (500 MHz, CDCl_3 , δ): 2.48 (t, $J = 2.1$ Hz, 1H), 3.17 (d, $J = 13.8$ Hz, 1H), 4.59 (d, $J = 13.8$ Hz, 1H), 4.70 (d, $J = 2.1$ Hz, 2H), 6.39 (s, 2H). ^{13}C NMR (125 MHz, CDCl_3 , δ): 32.14, 61.63, 75.53, 79.88, 118.87, 135.10, 136.79, 152.41. IR (neat, ν/cm^{-1}): 3295, 2921, 2195 (alkyne), 2104 (azide), 1587, 1529, 1467, 1366, 1314, 1232, 1201, 1001. HRMS: m/z : $[\text{M} + \text{NH}_4]^+$ calcd for $\text{C}_{40}\text{H}_{32}\text{N}_{13}\text{O}_4$, 758.2695; found, 758.2689.

Postsurface Modification of Immobilized Calyx[4]arene 6. Removal of the TBDMS protecting groups was conducted by submerging the GCE stub in a stirring solution of 1 M TBAF (10 mL); this reaction was run for 14 h. The electrode was removed from the solution and cleaned as described above. The CuAAC reaction of the unprotected alkyne with ferrocenylmethyl azide was achieved by immersing the stub in a rapidly stirred solution containing copper(II) sulfate (50 mg, 0.2 mmol) and sodium ascorbate (20 mg, 0.1 mmol); to this was added ethynyl ferrocene (10 mg, 0.05 mmol) dissolved in 2 mL of dichloromethane, and the reaction was run for 12 h. The GCE was then removed from the solution and cleaned before electrochemical analysis.

Post Surface Modification of Immobilized Calyx[4]arene 8. The postsurface modification of molecule 8 was conducted by submerging the GCE stub in a rapidly stirred solution containing copper(II) sulfate (50 mg, 0.2 mmol) and sodium ascorbate (20 mg, 0.1 mmol); to this was added the desired alkynyl (0.05 mol) dissolved in 2 mL of dichloromethane, and the reaction was run for 12 h. The GCE was then removed from the solution and cleaned before electrochemical or XPS analysis.

CONCLUSION

In summary, we describe two methods to form a monolayer of calix[4]arenes onto a GCE surface at either the upper or lower rims. These immobilized molecules have proven to be both chemically and electrochemically stable on an electrode surface, having up to four points of attachment to the surface per calixarene linker. These linkers can be easily functionalized by an array of substrates using the CuAAC reaction either before or after surface attachment with four points of modification per calixarene. The use of bifunctional Janus calixarenes offers a simple, yet highly versatile route to robust, multiattachment-point functionalization of surfaces for a wide range of potential chemical and biological species with applications ranging from analytical sensors through to heterogeneous catalyst support.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.langmuir.6b02222.

Synthesis, electrode modification procedures, and supplementary figures (PDF)

AUTHOR INFORMATION

Corresponding Authors

*E-mail: G.Wildgoose@uea.ac.uk.

*E-mail: P.Page@uea.ac.uk.

Notes

The authors declare no competing financial interest.

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