Spontaneous Aryldiazonium Grafting for the Preparation of Functional Cyclodextrin Modified Materials

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Abstract

A mild and efficient surface modification protocol for the preparation of β-cyclodextrin (βCD) modified surfaces through aryldiazonium mediated grafting is reported. Mono substituted 6-*O*-aminophenol-β-Cyclodextrin (amβCD) was synthesized through a three step protocol. This compound was found to form supramolecular aggregates in aqueous solutions at relatively low concentrations *via* cavity-directed self-assembly. Disruption of these supramolecular structures through judicious choice of solvent was found to be essential for the formation of the reactive

aryldiazonium species from the amino-phenolic precursor and for spontaneous surface grafting from aqueous solutions. Cyclodextrin thin films were prepared on carbon macroscopic substrates and electrodes and were characterized *via* infrared reflectance absorption spectroscopy (IRRAS), cyclic voltammetry and water contact angle measurements. Protein adsorption studies demonstrated that βCD adlayers reduced non-specific protein adsorption. βCD moieties in adlayers can be used nonetheless for specific host-guest complexation and are grafted at the surface with monolayer coverage (1.2×10^{-10} mol cm^{-2}) as demonstrated *via* experiments using ferrocene, a redox probe. Finally, cyclodextrin covalent immobilization was demonstrated also on stainless steel and polyamide samples, two substrates with wide ranging technological applications.

Introduction

Cyclodextrins (CD) are cyclic oligosaccharides most commonly consisting of 6 (α), 7 (β) or 8 (γ) glucose units linked together by a (1, 4) glycosidic bond. They possess a torus structure with a hydrophilic exterior, and a relatively hydrophobic cavity capable of forming host-guest inclusion complexes with a wide range of hydrophobic compounds.[1-2] The unique properties of cyclodextrins, coupled with their relative abundance and low-cost, render them extremely versatile and useful substrates with diverse applications in supramolecular chemistry, drug delivery, separation science, solubility enhancement and sensor technology.[3-5] In order to impart the desirable features of cyclodextrin onto surfaces, there exists a range of surface modification techniques including physisorption, chemisorption and covalent modification approaches, importantly, several of these approaches maintain the functionality of the cyclodextrin cavity on the surface and enable the design of functional materials with broad application. Surface

modification can be achieved *via* physisorption methods such as hydrogen bonding or through host-guest activity with surface expressed binding groups.[6] Physisorbed coatings generally display low stability and can typically be removed by physical displacement through sonication. More stable cyclodextrin surfaces can be achieved either by production of a polymeric deposition incorporating cyclodextrins,[1-2, 7-8] or through chemisorption, *i.e.* specific chemical modification to produce covalently bound cyclodextrins at the surface. Examples of this include grafting to cellulose *via* acid crosslinking,[9] production of gold surfaces modified *via* thiolene chemistry,[10] and electrochemical grafting of cyclodextrins onto conductive surfaces.[6, 11] Covalent immobilization of cyclodextrins has several benefits over physisorption and polymeric layer deposition, including coating stability and potential to retain surface properties and morphology. Spontaneous diazonium grafting is an attractive strategy for the production of a covalently modified cyclodextrin surface as it involves mild conditions, it is easily scalable and it is applicable to a wide variety of materials including carbon, polymer and metal alloy surfaces.[12-17] However, to the best of our knowledge there are no reports on the application of these spontaneous reactions to cyclodextrin immobilization. We have demonstrated previously that modification of surfaces through aryldiazonium chemistry with mono- and disaccharides is possible on a wide variety of materials including carbon and polymers.[13-14, 16, 18] The mono tosylation of the primary face (*i.e.* the 6' alcohol of the saccharide) opens up many avenues for cyclodextrin modification, [8, 19] including a potential pathway for producing a cyclodextrin diazonium salt-based grafting agent. Modification of the primary face to include an aromatic tail can however result in βCD in aqueous solution to readily form supramolecular host-guest complexes.[20-22] Complex formation can compromise the reactivity of aromatic tail groups *via*

inclusion in the cavity of neighboring βCD units and thus potentially prevent further reactions such as those leading to surface covalent grafting.

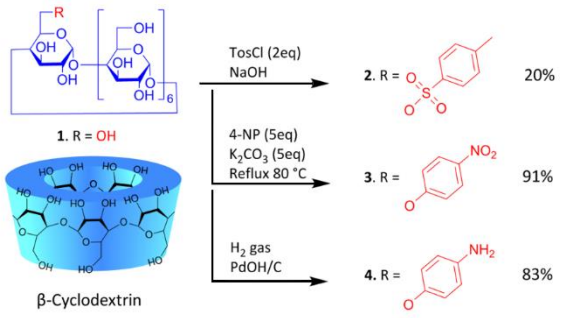
In this work we report the synthesis and characterization of a βCD-based aryldiazonium precursor molecule. We demonstrate that prevention of supramolecular host-guest assembly is essential for successful spontaneous surface grafting.[23-25] Disruption was achieved *via* cavity binding of a high affinity substrate such as adamantane or through modulation of the solvent polarity, with the latter method resulting in surfaces that display βCD-sites available for binding of organic substrates. Carbon materials were modified using aryldiazonium salts from these CD-glycosides in aqueous solutions and under mild conditions, resulting in glycosylated surfaces that display protein rejection behavior in the absence of specific host-guest interactions.[13, 16, 26] Cavity binding of surface-bound cyclodextrin was confirmed using a ferrocene/ferrocenium redox probe.[11] The functionalization method was then applied to two insulating surfaces of industrial interest: a metal alloy, stainless steel 316, and a polyamide, nylon-6, thus expanding the range of applications of this functionalization methodology.[26]

Results and discussion

Aryldiazonium precursor synthesis and characterization.

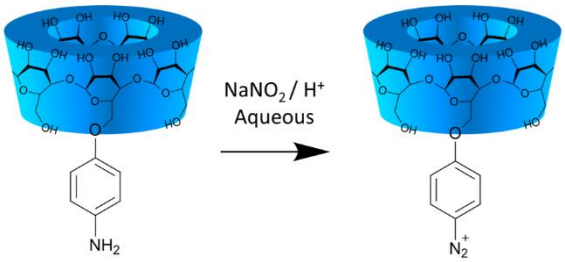
Mono substituted 6-*O*-aminophenol-β-Cyclodextrin (amβCD) was synthesized through a three step protocol outlined in Scheme 1. Beta-Cyclodextrin (βCD) 1 was mono-tosylated upon reaction with *p*-toluenesulfonyl chloride in alkaline solution.[19] The reaction mixture was neutralized through addition of 6 M hydrochloric acid and the resulting precipitate was filtered and repeatedly recrystallized from a 1:1 MeOH/H_2O mixture until a degree of tosylation (DT %) greater than 90% as determined by ^{1}H NMR was obtained.[27] The monotosyl-βCD 2 was

subsequently refluxed at 80 °C in the presence of excess p-nitrophenol in DMF to furnish the nitrophenolic derivative 3.[21] The desired aminophenol derivative 4 was prepared by hydrogenolysis of 3 in the presence of Pd on charcoal.[13]



Scheme 1. Synthesis of amβCD precursor sample in 3 steps.

Functionalization of carbon surfaces was first attempted *via* diazotization of amβCD under standard activating conditions (1 mM, aqueous $NaNO_2/H^+$), as indicated in Scheme 2, that are known to result in covalent grafting on carbon. However, these reactions were unsuccessful as no evidence of surface modification was observed. It was therefore hypothesized that self-assembly may lead to inactivation of the amino-phenolic tail thus preventing diazotization and/or covalent grafting of aryldiazonium cations.[13-14, 16, 18, 26]



Scheme 2. Aryl Diazonium Salt Formation.

This might occur if a neighboring cyclodextrin moiety complexes the amino-phenolic tail within the cavity leading to formation of supramolecular aggregates. In order to confirm that aggregation amβCD occurs in aqueous conditions at 1.0 mM, a solution of amβCD was prepared in ultrapure water with sonication, filtered through a 0.45 μm PES membrane filter and analyzed *via* dynamic light scattering (DLS) after a 1 h period of incubation at room temperature. DLS results are shown in the Supporting Information (Figure S1) and reveal scattering intensity equivalent to spherical particles with hydrodynamic radius >100 nm for amβCD at 1.0 mM. This indicates that aggregates of amβCD develop over 1 h at relatively low concentrations; identical experiments using unmodified βCD unit do not yield scattering intensity at hydrodynamic sizes >2 nm (Figure S1) in agreement with prior reports,[28] strongly indicating that aggregate formation is due to the presence of the amino-phenolic tails in amβCD. DLS experiments carried out under the same conditions but with addition of adamantane in 1:1 ratio with amβCD resulted in nearly identical stability to that of unmodified βCD, therefore indicating that the cavity-binding of the amino-phenolic tail is crucial to aggregate formation. Further evidence of involvement of amino-phenolic tails in the aggregation process was obtained from the ^{1}H NMR of aromatic protons of freshly prepared solutions of amβCD in D_2O, as shown for 1.2 and 3.0 mM concentrations in Figure 1a.

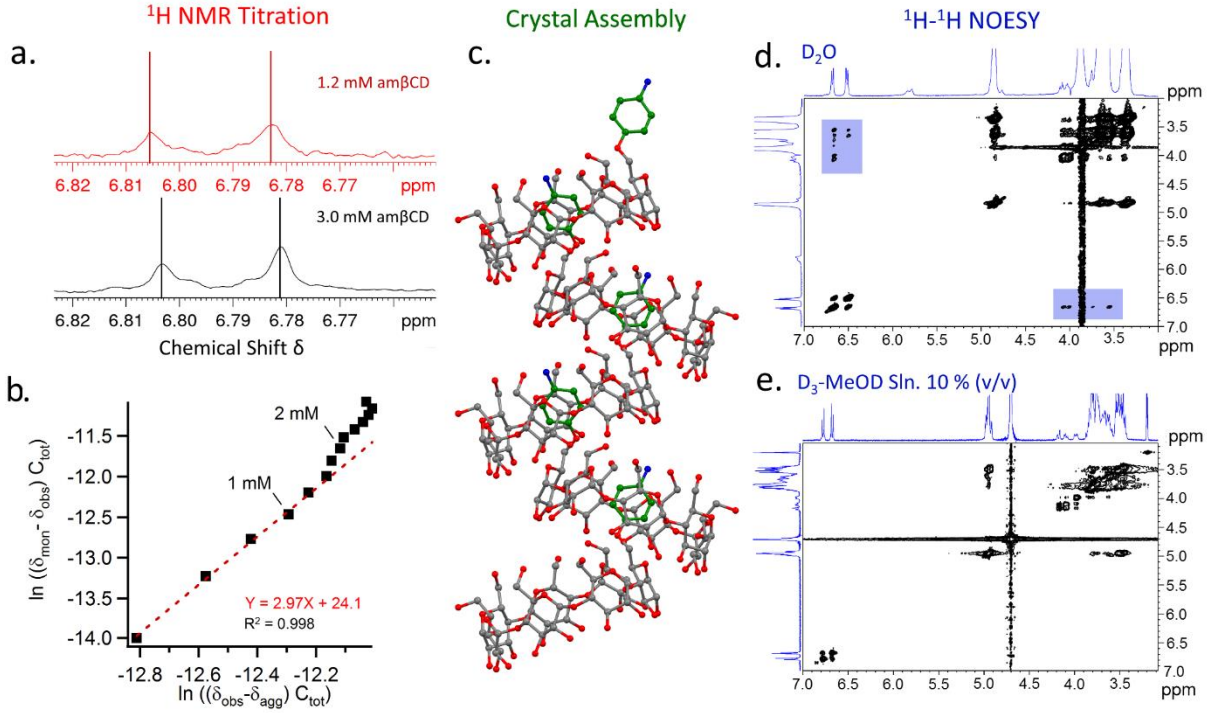


Figure 1. (a.) ^{1}H NMR (400 MHz) of amβCD in D_2O at 1.2 and 3.0 mM showing differing observed chemical shift of aromatic doublet, due to host-guest interactions. (b.) Plot of concentration components from eq. 1 for determining the aggregation number n from the slope; points represent measured data and the solid line is the best fit trend line. (c.) Illustration of the one-dimensional helical self-assembly of amβCD obtained by X-ray crystallography. Aromatic carbons have been highlighted (green); water of crystallisation and hydrogen atoms have been omitted for clarity. (d.) ^{1}H-^{1}H NOESY Spectrum of amβCD in D_2O; through space interactions between aromatic (tail) and saccharide (cavity) protons are highlighted in blue. (e.) ^{1}H-^{1}H NOESY Spectrum of amβCD in D_3-MeOD 10% v/v in D_2O. No interaction peaks are observed between aromatic (tail) and saccharide (cavity) implying negligible host-guest interaction under these conditions.

Spectra show a clear change in chemical shift indicating differences in the local environment of these protons at the two concentrations. This confirms that cavity directed self-assembly *via* host-guest interactions of the phenyl rings is important for the aggregation process. NMR

titration experiments were carried out over the concentration range 0.5-3.0 mM (Figure S2) and show a progressive change in the observed chemical shift (δobs) of aromatic protons. The δobs can be expressed as a function of the total concentration (Ctot), the relative chemical shift of the aromatic protons in monomeric βCD (δmon) and that of aromatic protons in the cavity of host-guest aggregates (δagg). Equation 1 shows the relationship between the association constant for the monomer-aggregate equilibrium of amβCD, Ka, the aggregation number n, and the relative chemical shifts, where δmon and δagg are determined by extrapolation (Figure S3). [20] For a detailed description of eq. (1) see Supporting Information.

$$\ln\left(C_{tot}(\delta_{mon}-\delta_{obs})\right) = n\ln\left(C_{tot}\left(\delta_{obs}-\delta_{agg}\right)\right) + \ln n - (n-1)\ \ln\left(\delta_{mon}-\delta_{agg}\right) + \ln K_a \qquad (1)$$

A linear fit of the concentration expressions from equation 1 (Figure 1b) yielded the aggregation number n = 2.97, confirming that this species forms trimeric structures at concentrations <1.5 mM. At higher concentrations it is possible to observe a second regime that suggests formation of larger aggregates (n>3). These findings are consistent with reports that show that dimerization results in further host-guest self-assembly in other phenyl-modified βCD species.20-22 From the intercept of the best fit to equation (1), a pKtri = -5.66 is obtained for the trimer equilibrium constant. Assuming a non-cooperative self-assembly process (pKn = (n-1) pK2, n ≥ 2), the dimer formation constant is estimated at pKdim = 2.83, or Kdim ≈ 680, in excellent agreement with phenyl-CD host-guest Ka values reported by Liu et al.[21]

Cyclodextrins displaying modifications with aromatic groups have been reported to form crystals *via* one of three pathways, cavity-tail self-inclusion, packed layers and one dimensional self-assembly.[20-22] Crystals of amβCD were grown from solutions in both D_2O and H_2O over 15 days at >3 mM concentration. X-ray crystallographic data analysis revealed that the compound crystallizes by aromatic tail penetration into the cyclodextrin cavity along a screw axis to form a linear head-to-tail supramolecular structure (Figure 1c). [21]These data confirm that self-assembly occurs *via* the insertion of the amino-phenol tail into the βCD cavity.

Results indicate that aggregate disruption is essential for the amino-phenolic tails to be available for further reactions. As shown by DLS, it is possible to achieve this *via* cavity-blocking with a high-affinity substrate such as adamantane. However, binding of such substrates effectively blocks the cavity, while it is more advantageous for further applications to achieve disruption by modulating solvent conditions while retaining an empty cavity. Nuclear Overhauser Effect (NOE) NMR spectroscopy was used to investigate the role solvent plays in supramolecular assembly. ^{1}H-^{1}H NOESY was performed on amβCD under various conditions. In D_2O (Figure 1d) strong interactions were seen between the aromatic protons at 6.8 and 6.6 ppm and the saccharide protons of the cavity, particularly the glycan H-5 and H-3 protons at peak positions 3.6 and 3.7 ppm, thus confirming host-guest interactions.[21] These peaks disappear upon selective cavity binding to adamantane (Figure S4) or when exposing the supramolecular assembly to a solvent system which contains a significant organic component, *i.e.* 10% v/v MeOH in water (Figure 1e). It was thus concluded that self-assembly behavior of compound 4 can be minimized either through pre-emptive host-guest binding or through careful modulation of solvent conditions.[23-24]

Carbon functionalization with βCD moieties.

Surface functionalization was carried out under conditions that promote disaggregation of 4 in solution while retaining a free cavity available for binding. Diazotization and surface grafting reactions were therefore carried out in 10% MeOH in aqueous solutions (Figure 2a): a 1.25 mM solution of amβCD was prepared in 1.25 mM HBF_4. This solution was then chilled to < 4 °C for 1 h, then diluted by addition of 0.010 M $NaNO_2$ to a final concentration of 1.0 mM βCD. Immediately after diazotization, the aryldiazonium cation solution was placed in contact with the substrate material, by either immersion or drop casting; the surface was kept in the dark for 1 h and subsequently rinsed and sonicated in methanol and water prior to characterisation.[13-14, 18, 26]

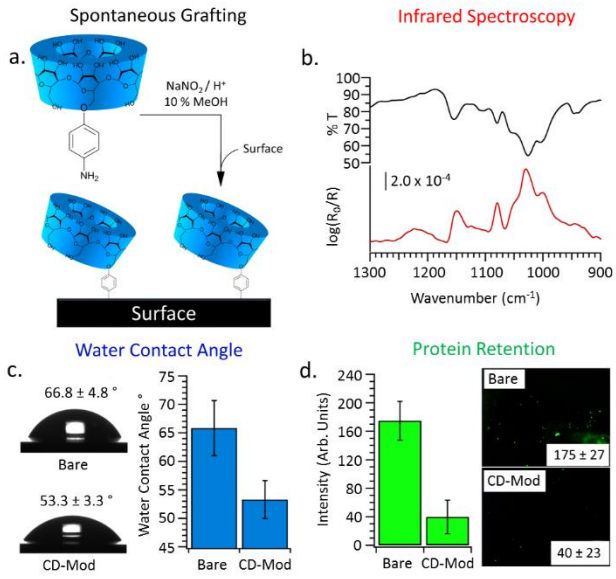


Figure 2. (a.) Schematic representation of surface modification. (b.) Infrared spectra showing transmittance spectrum of bulk amβCD diazonium precursor (top trace, black) and an IRRAS spectrum of a carbon surface after spontaneous grafting with βCD (bottom trace, red). (c.) Water contact angle (WCA) results for polished glassy carbon plates before (bare) and after (CD-Mod) functionalization with βCD; a significant decrease in WCA is observed after modification reactions. (d.) Protein adsorption studies on polished glassy carbon (bare) and on βCD-

functionalized carbon (CD-Mod) using FITC-BSA; values are average emission intensity after incubation in FITC-BSA solutions, while error bars represent 95 % CI.

Confirmation of spontaneous βCD grafting to amorphous carbon was obtained by ex-situ infrared reflectance absorption spectroscopy (IRRAS). Figure 2b shows the IRRAS of a carbon surface[29] modified *via* the process above. The transmittance spectrum of amβCD precursor compound in bulk form is also shown for comparison. Both spectra display characteristic peaks at 1145 cm^{-1}, 1080 cm^{-1}, 1024 cm^{-1} and 993 cm^{-1} corresponding to C-O stretching modes and O-H deformations of the carbohydrate rings.[30] The presence of these peaks is diagnostic for the presence of carbohydrate moieties at the carbon surface and is consistent with formation of a βCD adlayer. These peaks were not observed in the IRRAS of samples which had been immersed in a 10% MeOH solution of amβCD alone, without $NaNO_2$. Importantly, the peaks were also absent from samples immersed in an aqueous solution of amβCD and $NaNO_2/H^+$, but prepared without addition of 10% MeOH. The above control experiments indicate that both diazotization conditions and disruption of host-guest complex aggregates are essential to observe evidence of surface functionalization. Furthermore, they strongly indicate that βCD immobilization occurs *via* covalent bond formation by the reaction of the aryldiazonium cation with the carbon substrate.[13, 18, 26, 29]

Reaction of carbon with aryldiazonium cations of amβCD was also found to result in a significant change in surface wetting properties, consistent with the presence of a saccharide adlayer. Figure2c shows the water contact angle (WCA) of glassy carbon (GC) before and after functionalization. Results indicate that there is a significant decrease in WCA from (65.8 ± 4.8) ° (95 %CI) to (53.3 ± 3.3) ° (95 %CI). The increased hydrophilicity is attributed to increased surface density of hydroxyl groups resulting from grafting of βCD, and it is in agreement with

reported changes after modification with simpler mono- and di-saccharide moieties.[13-14, 18, 26] To investigate whether changes in wetting properties also affect interfacial interactions with biomolecules such as proteins,[13, 18, 26, 31-32] GC plates were incubated in buffered solutions of fluorescently labelled bovine serum albumin (BSA-FITC) at room temperature for 2 h. GC plates were rinsed and subsequently examined under microscopy with fluorescence excitation at 470 nm. The βCD-modified GC displayed lower FITC emission, thus indicating reduced protein retention when compared to unmodified samples (Figure 2d). These findings correlate well with WCA data and are consistent with previous findings on saccharide-modified surfaces.[13-14]

Surface host-guest binding.

βCD is known to form 1:1 inclusion complexes with ferrocene in solution,[11, 33] therefore ferrocene was used as a redox probe to investigate the surface density of βCD-sites and confirm availability of the surface-bound cavity to host-guest complexation. Two GC electrodes, one modified with βCD *via* the spontaneous reaction and one freshly polished, were immersed in a 5.0 mM solution of ferrocene in MeOH, rinsed and then tested *via* cyclic voltammetry (CV). Figures 3a and 3b show CVs obtained at 200 mV s^{-1} in 0.5 M KCl aqueous supporting electrolyte for the βCD-modified and bare GC, respectively.

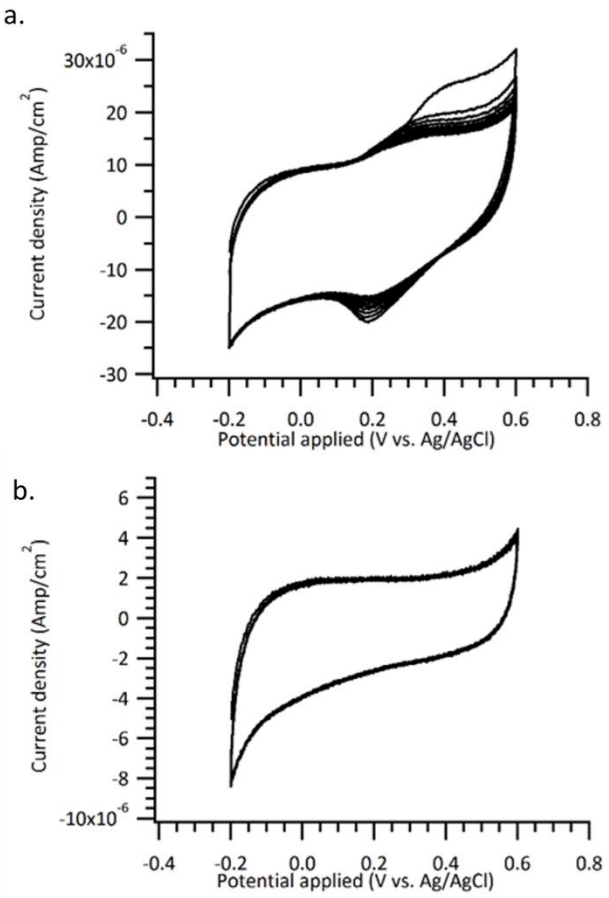


Figure 3. Cyclic voltammograms of CD-modified (a.) and bare (b.) glassy carbon electrodes after incubation in a 5 mM ferrocene solution in methanol, followed by rinsing. Voltammograms were obtained in 0.5 M KCl solutions at 200 mV s^{-1}.

GC electrodes modified with βCD (Figure 3a) display the characteristic oxidation and reduction peaks of ferrocene/ferrocenium (Fc/Fc^{+}) with a formal potential at 0.26 V vs. Ag/AgCl.[11] In contrast, in the absence of modification, the bare GC surface shows no evidence of faradaic peaks thus indicating that no significant amounts of ferrocene physisorb at bare GC. These results strongly suggest that the peaks observed in Figure 3a arise from specific CD-ferrocene binding interactions at the electrode interface. The first anodic sweep in Figure 3a is markedly different from that of subsequent cycles and its greater asymmetry suggests the presence of contributions from non-surface bound redox species. This behavior is likely to arise from small

amounts of weakly bound Fc^+ that is free to diffuse into solution. Peaks in subsequent cycles display instead symmetric peaks, whose intensity decreases slightly over multiple cycles. This is consistent with progressive partitioning of the more soluble Fc^+ species into the aqueous phase after each anodic sweep.[11] The total integrated charge associated with the anodic peak of the second cycle (0.2-0.5 V) was used to provide an estimate of surface coverage, Γ, for βCD-Fc complexes. Using equation (2) for a 1-electron transfer (n = 1), a scan rate ν = 0.2 V s^{-1} and an experimentally determined electrode geometric area[34] A = 0.196 cm^2:

$$\Gamma = \frac{Q}{nFA} = \frac{\int_{V1}^{V2} idV}{nFA\nu} \qquad (2)$$

The value of Γ obtained was 1.2×10^{-10} mol cm^{-2}. This value is in excellent agreement with Γ = 1.4×10^{-10} mol cm^{-2} calculated from crystallographic data for a hexagonal closed-packed layer of amβCD with its phenyl ring oriented normal to the carbon surface (see Supporting Information). This indicates that spontaneous aryldiazonium grafting of amβCD results in monolayer coverage. Further evidence for monolayer coverage was provided by atomic force microscopy measurements of the thickness of βCD adlayers, which yielded values consistent with the presence of a monolayer[35] (see Supporting Information). Monolayer control of aryldiazonium functionalization reactions is notoriously difficult to achieve, due to the tendency of these cations to cross-link yielding multilayers, particularly under electrografting conditions. The steric hindrance of the CD moiety is therefore likely to provide an intrinsic control mechanism for suppressing multilayer formation, as observed in previous studies on applications of bulky substitutents for monolayer control.[18, 36-40]

Functionalization of insulating surfaces.

One of the major advantages of spontaneous aryldiazonium reactions is the ability to impart surface functionality onto materials without the requirement of an electrical contact. This makes the spontaneous reaction a versatile method which was recently extended from the modification of conductors, e.g. carbon, Ni, Fe, Zn, [12] to the modification of polymeric insulators [13-14, 26] and oxide passivated alloy surfaces such as stainless steel.[17, 26] Therefore, we investigated the applicability of spontaneous grafting for the immobilization of βCD on nylon-6 and stainless steel 316 (SS316), a polymeric and an alloy material of importance for a wide range of applications. Nylon-6 samples were pre-treated *via* formaldehyde activation, while SS316 coupons were subject to an oxidative activation treatment.[26] Samples were subsequently immersed in solutions of the aryldiazonium cation from amβCD, as in Figure 2a. Figure 4a and 4b show the resulting WCA values obtained on nylon-6 and SS316 both prior to, and post immersion in the aryldiazonium grafting solution.

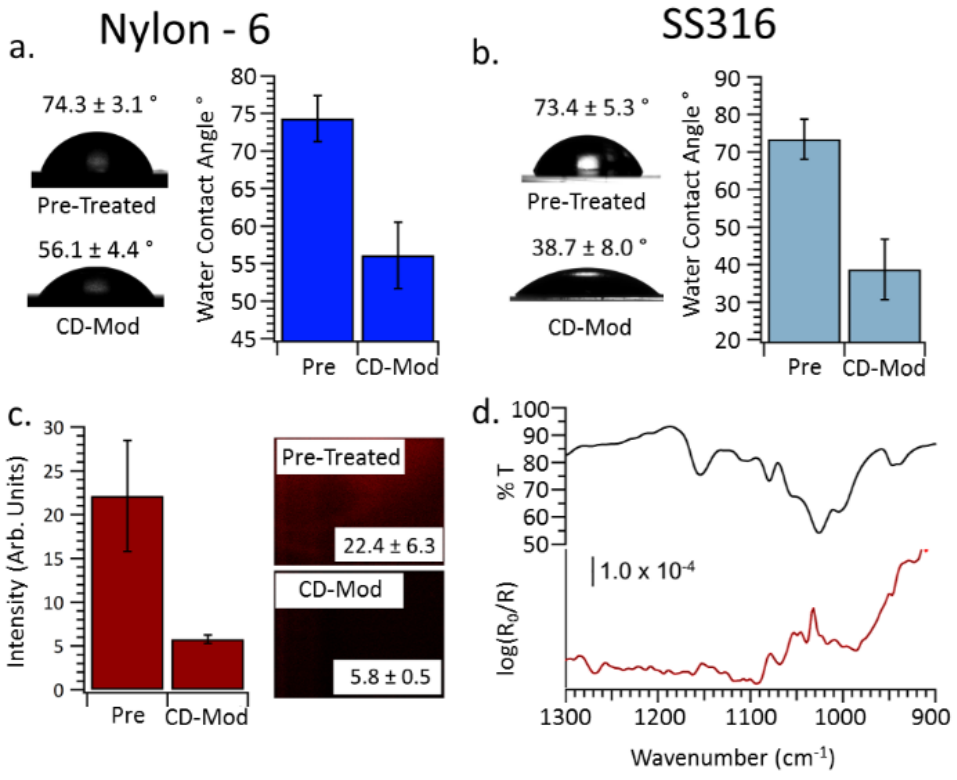


Figure 4. Water contact angles for nylon-6 (a.) and SS316 (b.) before and after spontaneous reactions with aryldiazonium cations from amβCD. (c.) Protein adsorption tests on nylon-6 using fluorescently labelled BSA (Alexa-BSA); the bar chart shows average emission intensity measured after incubation in Alex-BSA solutions on surfaces before and after modifications. (d.) IRRAS spectrum obtained on SS316 after functionalization reactions with βCD; the transmittance spectrum of amβCD is shown in the graph for comparison.

In all cases, hydrophilicity increased, as expected after modification with βCD adlayers. The effect on protein adsorption resulting from βCD grafting on nylon-6 was also characterized using buffered solutions of BSA labelled with Alexa Fluor-647. After incubation in such solutions the total emission arising from adsorbed protein is lower in the case of nylon-6 modified with βCD (Figure 4c). The IRRAS spectrum obtained from SS316 surfaces after modification with βCD is shown in Figure 4d. The spectrum compares well with the one obtained in transmittance from the precursor amβCD. These experiments therefore confirm that the spontaneous reaction results in grafting of βCD functional moieties on materials with a wide range of properties.

Conclusions

We have demonstrated that a synthetic p-nitrophenol cyclodextrin substrate, prepared from native β-cyclodextrin *via* a three step synthesis is suitable for aryldiazonium grafting onto a range of materials. The synthesized CD-derivative aggregates in solution, at relatively low concentrations, *via* cavity directed self-assembly. We demonstrate that disruption of these aggregates is essential for successful functionalization and that this can be achieved *via* cavity binding with high-affinity substrates or *via* modulation of solvent properties. The latter method was leveraged to achieve spontaneous grafting of βCD groups. The resulting adlayers were found

to be hydrophilic and to reduce protein retention, while the binding properties of βCD moieties were preserved once covalently linked to the surface. This suggests that these βCD adlayers can potentially play a dual role in reducing non-specific binding to biomolecules, while presenting a binding cavity available for leveraging specific host-guest interactions. Importantly, the specific route to surface immobilization reported in this work yielded closed-packed monolayers of βCD, a feature that is important e.g. for effective control of assay sensitivity in βCD sensing applications. It is anticipated that this approach will find widespread application in the preparation of cyclodextrin surfaces as the process is readily scalable, and applicable to a wide range of polymeric, alloy and carbon surfaces.

Conflicts of interest

The authors declare no conflicts of interest.

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SUPPORTING INFORMATION

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Experimental procedures for cyclodextrin modification, DLS, NMR and X-Ray data for aggregation studies, monolayer thickness and coverage estimates and ^{1}H- and ^{13}C-NMR Spectra of modified cyclodextrins.

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