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m-Terphenyl thiols: rigid and bulky molecules for the formation of bioactive self-assembled monolayers on gold†

Diane A. Dickie,[a] Andy Y. C. Chan,[a] Hanifa Jalali,[a] Hilary A. Jenkins,[b] Hua-Zhong Yu*[a] and Jason A. C. Clyburne*[a]

[a] *Department of Chemistry, Simon Fraser University, Burnaby, British Columbia, V5A 1S6, Canada. E-mail: clyburne@sfu.ca; hzyu@sfu.ca; Fax: +1 604 291 3765*

[b] *Department of Chemistry, Saint Mary's University, Halifax, Nova Scotia, B3H 3C3, Canada*

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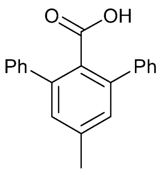
The *m*-terphenyl 4-mercaptomethyl-2,6-diphenylbenzoic acid (3), was prepared and shown to form ω-carboxyl terminated self-assembled monolayers (SAMs) on gold with high surface pK_a (10.1 ± 0.2) and low density favourable for the binding of biological macromolecules.

The chemisorption of ω-carboxyl terminated organosulfur compounds on gold surfaces is used extensively to form self-assembled monolayers (SAMs). These structurally well-defined organic surfaces are of interest for applications in chemistry, biology, surface science, sensor development, and nanomaterials.[1] For example, this type of SAM can be used as a starting point for immobilising proteins or other biological macromolecules for analysis.[2] The most common organosulfur compounds used in SAM formation are ω-functionalised alkanethiols.[3] Rigid thioaromatic molecules[4] such as *p*-terphenyls are also used due to their potential for electrical conductivity from π-conjugation.[5]

Both alkyl and aryl thiols form well-organised, closely-packed monolayers. In many applications involving biological macromolecules or other large analytes, it is advantageous to have a low-density surface in which the ω-terminal functionality is isolated from its neighbours to prevent aggregation and undesired steric restrictions. A common approach for achieving this goal is to shorten the immersion time of the substrate in the deposition solution.[6] This method offers very little control over the arrangement of and the environment around the ω-terminal functional groups on the SAM. It has been shown that the chemical and physical properties of surfaces are dependent on structure;[7] such imprecision may be detrimental to many applications.

Recently, two groups have developed new routes to prepare low-density monolayers. Lahann[8] *et al.* designed alkanethiols with bulky head groups while Liu[9] *et al.* used substituted alkanethiols wrapped with cyclodextrins. After the monolayer has formed, the head group or cyclodextrin can be removed to leave isolated ω-carboxyl terminated alkyl chains. Our straightforward synthesis of a sterically demanding molecule that directly attaches to the surface and gives a low density of ω-carboxyl groups is a more atom-efficient route to such functionalised surfaces.



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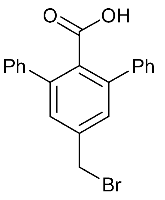

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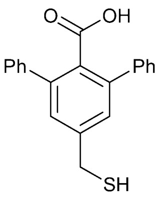

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m-Terphenyls are molecules with two aryl substituents *meta* to one another on a central phenyl ring.[10] The aryl substituents twist out of the plane of the central ring to create a bowl-shaped pocket whose steric demands can be tuned by varying the nature of the aryl groups. The rigid and bulky nature of *m*-terphenyl molecules[11] make them ideal for the formation of SAMs with inherently low density ($<1.4 \times 10^{-10}$ mol cm^{-2}), as each molecule occupies an area of *ca.* 112 Å^2 (Fig. 1),[12] comparable to the density of cyclodextrin-modified surfaces.[9] In addition, because each carboxylic acid group is isolated within an individual hydrophobic pocket, a high acid-dissociation (pK_a) on the surface would be expected,[13] *i.e.* the carboxyl group would be in the protonated form over a large pH range. This is desirable because many biological macromolecules attach to the surface *via* amide or hydrogen bond formation.

The radical bromination of 4-methyl-2,6-diphenylbenzoic acid **1** with NBS gives 4-bromomethyl-2,6-diphenylbenzoic acid **2**.[14] This molecule reacts with thiourea to give 4-mercaptomethyl-2,6-diphenylbenzoic acid **3**. The ^{1}H NMR spectrum shows a triplet at 3.08 ppm and a doublet at 3.81 ppm due to the S*H* and C*H*$_2$ respectively. The IR spectrum shows a strong ν(C=O) absorption at 1693 cm^{-1}.

The *m*-terphenyl SAMs were formed by the immersion of clean gold substrates for 24 hours in deoxygenated 1.0 mM 9:1 ethanol-acetic acid solutions of **3**. The addition of acetic acid is essential as it decreases the hydrogen-bonded dimerisation of **3** in solution.[3,15] The substrate was washed sequentially with solvent mixture and deionized water to remove any unbound molecules. The FTIR spectrum of the modified gold substrates (Fig. 2A) shows peaks that are consistent with the formation of a SAM of **3**. Most importantly, the ν(C=O) absorption at 1671 cm^{-1} confirms the presence of the carboxyl functionality on the surface. Peaks for ν(C–O) are present at 1148 and 1092 cm^{-1} and C–C aromatic stretches from the *m*-terphenyl are seen at 1594 and 1466 cm^{-1}. In contrast to long chain *n*-alkanethiolate SAMs, the bands in the region of 2700–3200 cm^{-1} corresponding to CH$_2$ streches are rather weak because only one methylene group is present in the

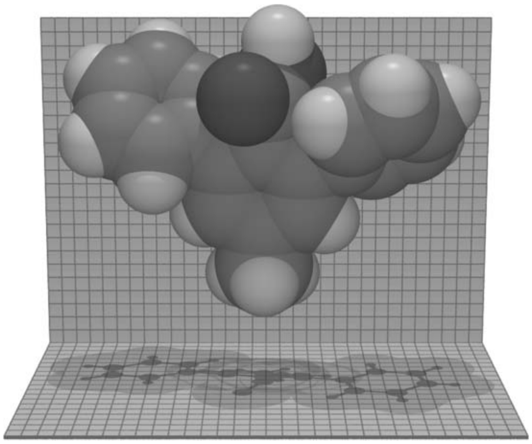

Fig. 1 Solid state (space filling) model of **1**, including the shadow cast on a surface. The grid size is 0.5 Å.

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† Electronic supplementary information (ESI) available: Synthetic procedures and characterisation data for **1–3**, and X-ray crystallographic data in .cif format for **1**. CCDC 244469. See http://www.rsc.org/suppdata/cc/b4/b410264a/

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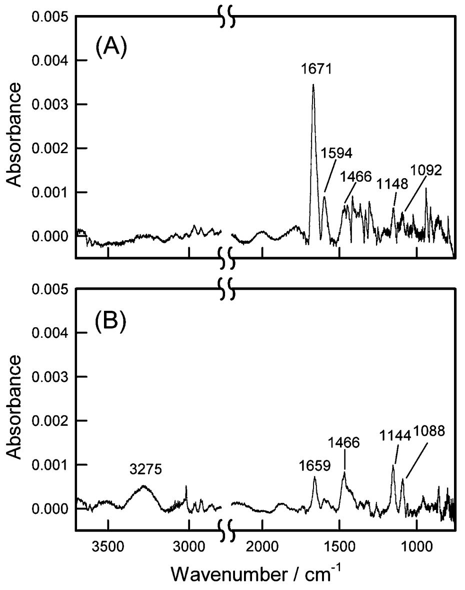

Fig. 2 FTIR spectra of *m*-terphenyl SAMs formed from the adsorption of **3** on gold (A) and after futher reaction with adenine/THF solution (B).

m-terphenyl thiol **3**. The low-density packing of the molecules in the SAM also reduces the signal intensity.

The reactivity of our *m*-terphenyl SAM was demonstrated by the treatment of the monolayer with a THF solution of adenine (2.7 mM). Adenine forms hydrogen bonds with the carboxyl group on surface and significantly changes the FTIR spectrum (Fig. 2B). The most obvious change is the appearance of a band at 3275 cm^{-1} for the NH stretch. The peak at 1466 cm^{-1} with shouders may be attributed to both C–C aromatic stretches (*m*-terphenyls) and imidazole ring streches (adenine, at 1453 cm^{-1}). Another change upon binding of adenine is the shift of the carboxyl C=O stretch from 1671 to 1659 cm^{-1} and the C–O stretches from 1148 and 1092 cm^{-1} to 1144 and 1088 cm^{-1}, respectively. The clear decrease of the overall absorbance in Fig. 2B in comparison with Fig. 2A also indicates the formation of an additional layer of molecules on top of the SAMs of **3** on gold.

Wetting measurements were used to further characterise the SAM of **3** on gold. At high pH, carboxyl-terminated surfaces become more hydrophilic due to the formation of the carboxylate anion and show decreased contact angles. Conversely, as the pH decreases, the protonated surface becomes more hydrophobic and contact angles increase. The plot of contact angle versus pH represents a typical titration curve of surface carboxyl groups (Fig. 3). The pK_a of the surface was evaluated by fitting the experimental data with the help of previouly developed procedures.[13] To minimise errors associated with salt formation on the surface by different buffers and to ensure reproducibility, measurements were repeated on several spots on different samples. The pK_a of the SAM of the *m*-terphenyl **3** on gold was found to be 10.1 ± 0.2, significantly higher than that of similar *m*-terphenyl carboxylic acids in solution (6.39).[16] It should be also noted that both the protonated and deprotonated forms of the surface are not completely hydrophilic, which would be expected for a surface that was completely covered by carboxyl groups (*e.g.*, 11-mercaptoundecanoic acid SAMs). This indicates that the surface density of carboxyl groups is relatively low and they are isolated by the hydrophobic terphenyl moeities.

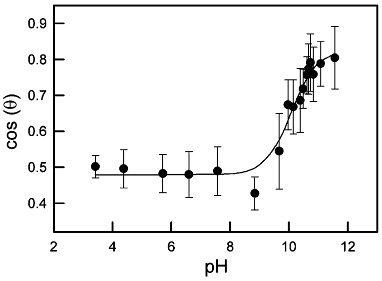

Fig. 3 Contact angle titration curve of *m*-terphenyl SAMs prepared from the adsorption of **3** on gold, measured using a nonreactive spreading protocol.

In conclusion, a rigid and bulky carboxyl-terminated *m*-terphenyl thiol was synthesised and was demonstrated to form self-assembled monolayers on gold. These SAMs have a pK_a of 10.1 ± 0.2 and the well-isolated carboxyl groups can undergo further reactions with biomolecules as shown by reaction with adenine.

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