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# Synthesis of a *cone*-conformer bimodal calix[4]arene-crown-5 which forms a sensitive cesium ion sensing layer on gold-coated microcantilevers

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The synthesis of a "bimodal" or upper- and lower-rim functionalized "calix-crown-5" reported herein unexpectedly was formed preferentially in a *cone* conformation. This was confirmed both by NMR spectroscopy and by a single-crystal X-ray crystallography. The thioacetate functionalities on the new calix-crown-5 enabled it to form stable SAMs onto the Au surface of a microcantilever, and was a sensitive cesium ion sensor.

## 1 Introduction

Calixarenes are well-known and widely-reported chemical entities since, along with other macrocyclic compounds such as, for example, resorcinarenes, cyclotrimeratrylenes and cyclodextrins they are key molecular building blocks which have been widely used in supramolecular chemical studies.<sup>1</sup> The "classical" calix[*n*]arenes (*n* = 4, 6 or 8) which have their 4, 6 or 8 phenolic rings bridged by the same numbers of methylene groups are easily synthesized by the condensations of *p*-*tert*-butylphenol and formaldehyde under the alkaline conditions which were meticulously described by the pioneering work of Gutsche and coworkers.<sup>2</sup> The general strategy used to exploit the important applications of these molecules, which include sensing<sup>3</sup> and separation<sup>4</sup> of metal ions and organic molecules<sup>5</sup> has relied on the modification of either, or both, the upper<sup>6</sup>- and lower<sup>7</sup>-rims of the parent calixarenes.

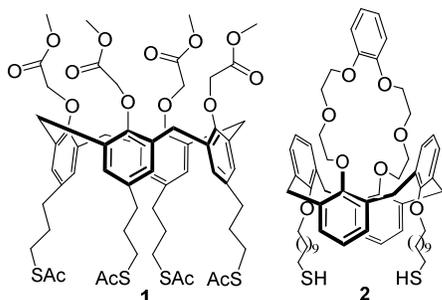


Fig. 1 Structures of *cone*-1 and 1,3-*alternate*-2.

Our own interest in using the scaffold provided by calix[4]arene has been to develop upper- and lower-rim bimodal derivatives for their use as sensing layers on Au microcantilevers (MCLs).<sup>8,9</sup>

Our earlier work reported on the synthesis and properties of calixarene **1** (Fig. 1) in which the upper-rim contained thioacetate,<sup>8</sup> and the lower-rim *O*-(methoxycarbonyl)methoxy functional groups. The thioacetate groups<sup>11</sup> allowed the anchoring of **1** onto the Au layer of a MCL, and the ester groups enabled the sensitive detection by the MCLs of Ca<sup>2+</sup> ions in aqueous solutions. Ji *et al.*, had previously reported the 1,3-*alternate* conformer calix[4]arene **2** which was functionalized with a benzocrown-6 ether linking the 1,3-positions of the lower-rim and the remaining lower-rim positions functionalized with 11-mercapto-1-undecanoyl ethers.<sup>3a</sup> Their calixarene formed a stable self-assembled monolayer (SAM) onto the Au surface of a MCL resulting in a selective receptor for Cs<sup>+</sup> ions.

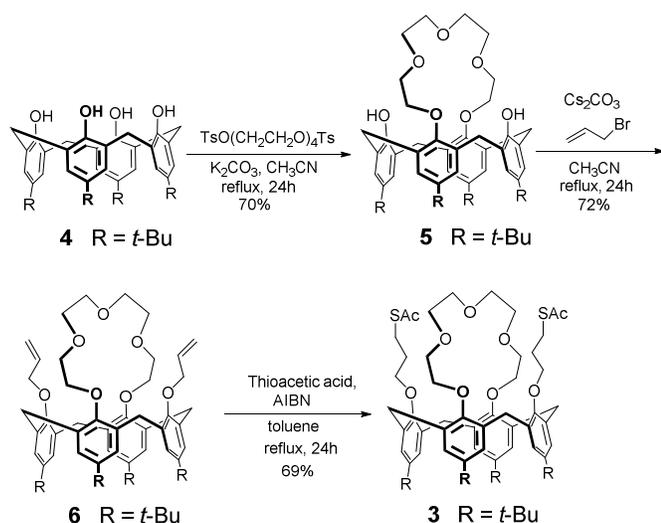
As part of our on-going studies of potential calixarene-based sensing layers for MCLs, we report herein the synthesis of a new 1,3-bridged-"crown-5" thioacetate-bearing calix[4]arene **3** which also forms a SAM on a Au-coated MCL and which also binds selectively to Cs<sup>+</sup>. As with **1**, the thiolate groups on one pair of the *distal* or 1,3-positions of the lower-rim, enables **3** to form a stable SAM on the Au surface of the MCL. The other lower-rim "crown-5" group selectively binds to Group 1 (alkali metal), cations, in aqueous solutions. Unlike **2** however the new crown calixarene **3** is in a *cone* conformation. Presented herein also is the single-crystal X-ray crystallography of **3**.

## 2. Experimental section

### 2.1 Materials and instruments used

All reagents used for the syntheses of the calixarenes **3-6** and reagents used in the complexation studies were purchased from Sigma-Aldrich or AlfaAesar. <sup>1</sup>H-NMR spectra were recorded at either 300 or 500 MHz, as noted, and for the <sup>13</sup>C-NMR spectra

at 75 MHz as noted. Mass spectra were conducted on an APCI-LC/MSD Trap instrument.



**Scheme 1** Reaction scheme for the synthesis of **3**

## 2.2 Conditions for the synthesis of calixarenes **3** and **6**

**Calixarene 6:** To a solution of calix[4]arene **5**<sup>11</sup> (1.0 g 1.2 mmol) prepared from **4**,<sup>2</sup> in acetonitrile (50 mL) was added Cs<sub>2</sub>CO<sub>3</sub> (1.61 g, 4.96 mmol) and the reaction mixture was heated at reflux for 30 min. Allyl bromide (0.42 ml, 5.0 mmol) was added to the reaction mixture and heated at reflux for 24h. After cooling to room temperature, the reaction mixture was neutralized with 1.0 M HCl<sub>(aq)</sub>, then extracted with ethyl acetate (3×100 mL) and washed with water (2×50 mL). The separated organic layer was dried over anhydrous MgSO<sub>4</sub> and the solvent was removed using a rotavap. The residue was purified by column chromatography (silica gel, eluting with hexane:ethyl acetate 70:30 to give **6** (792 mg, 72%, m.p. 120.1-121.3°C) as a colourless solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ = 7.03 (s, 4H, ArH), 6.53 (s, 4H, ArH), 6.36 (m, 2H, CH=CH<sub>2</sub>), 5.33 (d, J=18 Hz, 2H, CH=CH<sub>2</sub>), 5.22 (d, J=18 Hz, 2H, CH=CH<sub>2</sub>), 4.38 (m, 8H, -OCH<sub>2</sub>Ar and ArCH<sub>2</sub>-), 4.20 (s, 8H, -OCH<sub>2</sub>-), 3.78 (m, 8H, -OCH<sub>2</sub>-), 3.13 (d, 4H, J=15 Hz, 4H, ArCH<sub>2</sub>-), 1.26 (s, 18H, *t*-Bu), 0.88 (s, 18H, *t*-Bu). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75.45 MHz): δ = 154.7, 152.0, 144.9, 144.3, 135.7, 134.9, 132.5, 125.3, 124.53, 117.6, 72.6, 71.6, 71.4, 70.2, 34.0, 33.7, 31.6, 31.3, 31.2. APCI (+) MS(*m/z*): 887.5 (M<sup>+</sup>).

**Calixarene 3:** A solution of **6** (500 mg, 0.6 mmol), thioacetic acid (0.26ml, 3.4 mmol) and 2,2'-azobis[(2-methyl)propanenitrile] (AIBN) (9 mg, 0.06 mmol) in toluene (30 ml) was degassed and then stirred at reflux temperature for 24h under N<sub>2</sub>. After cooling to room temperature, the solvent was removed using a rotavap. The residue was dissolved in ethylacetate (100 mL), and washed with water (50 mL). The organic layer was separated and dried over anhydrous MgSO<sub>4</sub> and filtered. The solvent was removed using a rotavap and the residue was purified by column chromatography (silica gel, eluting with hexane:ethyl acetate 60:40 to give **3** (407 mg, 69%, m.p. 194.5-195.3 °C) as a colourless solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>,

300 MHz): δ = 7.10 (s, 4H, ArH), 6.43 (s, 4H, ArH), 4.29 (d, J = 12.6 Hz, 4H, ArCH<sub>2</sub>-), 4.20 (m, -OCH<sub>2</sub>Ar), 3.78 (m, 12H, -OCH<sub>2</sub>- and ArOCH<sub>2</sub>-), 3.13 (m, 8H, ArCH<sub>2</sub>-; -CH<sub>2</sub>CH<sub>2</sub>SCO-), 2.33 (s, 6H, -SCOCH<sub>3</sub>), 2.20 (t, 4H, -CH<sub>2</sub>CH<sub>2</sub>SCO-), 1.33 (s, 18H, *t*-Bu), 0.804 (s, 18H, *t*-Bu). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75.45 MHz): δ = 195.7, 154.7, 152.0, 145.1, 144.2, 135.2, 131.6, 125.6, 124.6, 74.2, 72.5, 71.2, 70.3, 34.1, 33.6, 31.7, 31.1, 31.0, 30.7, 26.3. APCI(+) MS(*m/z*): 1039.5 (M<sup>+</sup>).

## 2.3 X-ray crystallography of **3**

Slow evaporation of a solution of **3** in acetonitrile and ethanol formed crystals of **3** which crystallized in the monoclinic space group P2<sub>1</sub>/n, with three chemically identical molecules in the asymmetric unit. The molecules packed in discrete chains perpendicular to the *c*-axis, though no significant intermolecular interactions are present. Each molecule adopts a *cone*-like configuration (Fig. 2). The ether chains and bridge exhibited disorder in the crystal structure that was difficult to model, however, this disorder did not indicate the presence of any molecules in the *1,3*-alternate conformation. Detailed crystallographic data is provided in a cif file in the Supporting Information.

## 2.4 Preparation of the microcantilevers

Microcantilever sensors used in this work (MikroMasch, CSC38/tipless/No Al) were approx. 350 μm × 32.5 μm and 1-μm thick with a nominal spring constant 0.03 N·m<sup>-1</sup>. In order to clean the cantilever and ensure the complete removal of organic residue, oxide layer, and ionic contaminants, MCLs were treated with the RCA cleaning method as described previously.<sup>8</sup> The MCLs were subsequently coated with a 5-nm thin film of Inconel (0.8Ni:0.2Cr) used as an adhesion layer followed by a 40-nm thin film of Au both deposited by sputter deposition. MCLs were then functionalized for 1 h in a dichloromethane:ethanol (1:9) solvent solution of **3** (1.0 × 10<sup>-6</sup> M), to form SAMs on the Au surface of the MCLs. These MCLs are referred to as the “active MCLs”. All experiments conducted during this work were performed with the use of a reference MCL used to exclude deflections due to thermal and mechanical sources that may affect the signal of the active MCL. The signal of the reference MCL is subtracted from the signal of the active MCL to give the differential signal providing a measure of the MCL deflection caused only by the interaction between **3** and the target ions. The reference MCLs were subjected to the same cleaning and films deposition procedures as the active ones. The reference MCLs were prepared by incubating Inconel/Au-coated MCLs in a 1.0 μM solution of decanethiol for 1 h.

## 2.5 Microcantilever experimental setup

Once coated, both the active and reference microcantilevers were placed into the fluid cell which is part of our experimental setup. The system used in our work has been discussed in greater detail elsewhere.<sup>12</sup> Briefly, the fluid cell is connected to two polyether ether ketone PEEK tubes, which are responsible for transporting the solution from a syringe pump in and out of

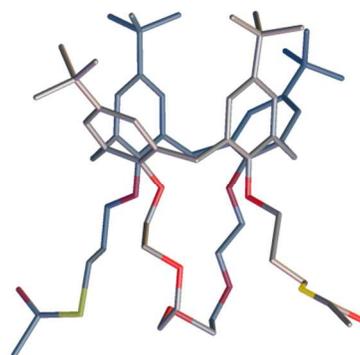
the fluid cell. Outside the cell, optical beams are focused on the free end of the microcantilevers through a window using optical focusers. The reflected beams from each microcantilever are directed into two separate linear PSDs used to monitor the deflection of the cantilevers. At the onset of our experiments, research-grade distilled water was injected at a flow rate of 0.1 ml/min until a steady baseline was obtained. This baseline indicates that the calixarene-functionalized microcantilevers have reached a thermal equilibrium with the fluid cell at which point the target molecules were injected and the deflections monitored.

### 3. Results and discussion

The synthesis of **3** is shown in Scheme 1. 1,3-Calix[4]-crown5 (**5**) was first synthesized according to the procedure of Chailap and Tuntulani<sup>10</sup> from *p*-*tert*-butylcalix[4]arene (**4**).<sup>2</sup> From the published literature on similar transformations on calix[4]arenes similar to **5** it was anticipated that its reaction with allyl bromide in the presence of Cs<sub>2</sub>CO<sub>3</sub> in acetonitrile would have resulted in the corresponding *1,3-alternate* conformer of **6** and hence subsequently to the formation of the corresponding *1,3-alternate* conformer of **3**. However, we were able to confirm that the major product obtained from this reaction was in fact, the *cone* conformer **6**, which can be produced reproducibly in 72% yields. All of the newly-synthesized compounds were characterized by <sup>1</sup>H-, <sup>13</sup>C NMR, and mass spectrometry, and in the case of **3**, by single-crystal X-ray crystallography. All of the spectra are presented in the Supporting Information.

The spectra of **6** suggested that the calix[4]arene unit is in a *cone* conformation since the proton chemical shifts of the bridging –CH<sub>2</sub>– groups, appeared as a pair of AB doublets, each of which is centred at  $\delta$  4.37 and 3.14 ppm ( $J=15$  Hz), and the <sup>13</sup>C chemical shifts at  $\delta$  34.0 ppm, positions which are typical of a calix[4]arene in a *cone* conformation. The *tert*-butyl groups appear as two 18-proton singlets at  $\delta$  = 1.26 and 0.88 ppm. The <sup>1</sup>H NMR spectrum of **3** which is derived by thioacetylation of the terminal alkenes of **6** with thioacetic acid by a procedure previously reported both by us<sup>8</sup> and Kimura *et al.*<sup>13</sup> reveals the chemical shifts of the bridging –CH<sub>2</sub>– groups as a pair of AB doublets each of which is centred at 4.30 and 3.15 ppm ( $J=14$  Hz); and in the <sup>13</sup>C-NMR spectrum at  $\delta$  = 34.1 ppm positions, as noted for **6**, which are typical of other calix[4]arenes in *cone* conformations. The *tert*-butyl groups appear as two 18-proton singlets at  $\delta$  = 1.33 and 0.80 ppm. The NOESY spectra of either **3** and **6**, however, were inconclusive. A single-crystal X-ray analysis of **3** however unequivocally showed it to be in a *cone* conformation (Fig. 2)<sup>14</sup> and this in agreement with the postulated <sup>1</sup>H NMR interpretations.

Other conditions which were tested in attempts to produce the *1,3-alternate* conformer of **6**, namely NaH in THF, or Na<sub>2</sub>CO<sub>3</sub> in acetone, at reflux conditions, also only produced the same *cone* conformer **6**. Presumably, the relatively smaller



steric bulk of the allyl ether groups did not lead to the preferential formation of the *1,3-alternate* conformers as seen with other bulkier *1,3*-lower-rim substituent groups, when introducing the crown-5 ether component

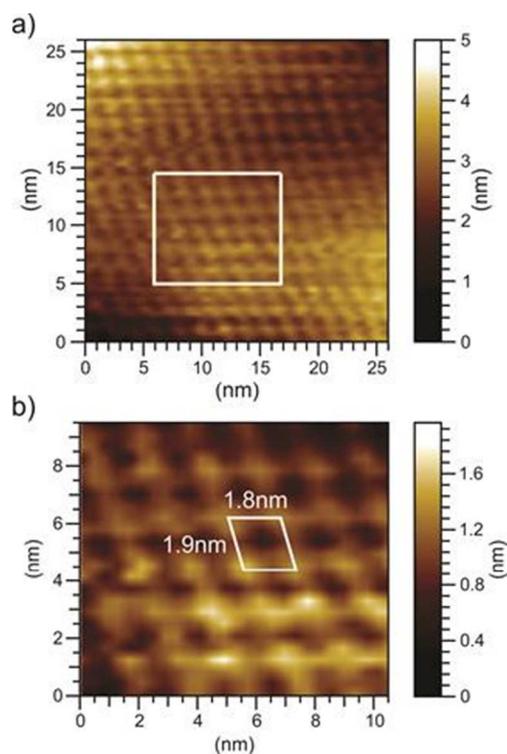
**Fig. 2:** A single molecule of **3**, represented as capped sticks, showing the *cone* conformation. H-atoms and minor disorder components were omitted for clarity.

#### 3.1 Self-assembled monolayer on Au-coated microcantilever studies

Since the objective for the synthesis of **3** was to test its suitability as a selective metal ion sensing layer within the crown ether moiety of **3** in a Au-coated microcantilever application, typically in aqueous solutions, STM imaging was performed in order to assure that this new calixarene **3** was capable of adhering to a Au surface. Samples for imaging were prepared as described previously.<sup>8</sup> Fig. 3a) shows a 26 × 26 μm<sup>2</sup>-sized image of molecules of **3** on the gold surface clearly indicating the presences of a highly-ordered SAM of the bimodal calixarene molecules. A 9.5 × 10.5 μm<sup>2</sup> section of this figure was isolated and expanded as shown in Fig. 3b). In order to help highlight the molecular ordering, the image was processed using the Scanning Probe Image Processor (SPIP) software. This image more clearly reveals the high ordering of calixarene molecules on the MCL surface, indicating the sensing layer is well-established on our cantilevers which should be very stable due to the strong bonding between the sulphur atoms and gold substrate.<sup>15</sup> With each high spot in the image indicating a single calixarene molecule, the intermolecular distances have been measured to be 1.9 nm and 1.8 nm in the directions shown in the figure. These values are consistent with similar observations made with other types of calixarene-based SAMs e.g. Pan *et al.*<sup>16</sup> and us, previously.<sup>8</sup>

Fig. 4a) shows the deflections of calixarene **3**-coated MCLs to four different aqueous (5.0 μM) metal chloride solutions. Since we had previously noted significantly greater responses to chloride counterions in the case of calcium halides with the thioacetate-calixarene **1**,<sup>8,9</sup> aqueous solutions of CaCl<sub>2</sub>, KCl, RbCl and CsCl were tested. The largest deflections seen were

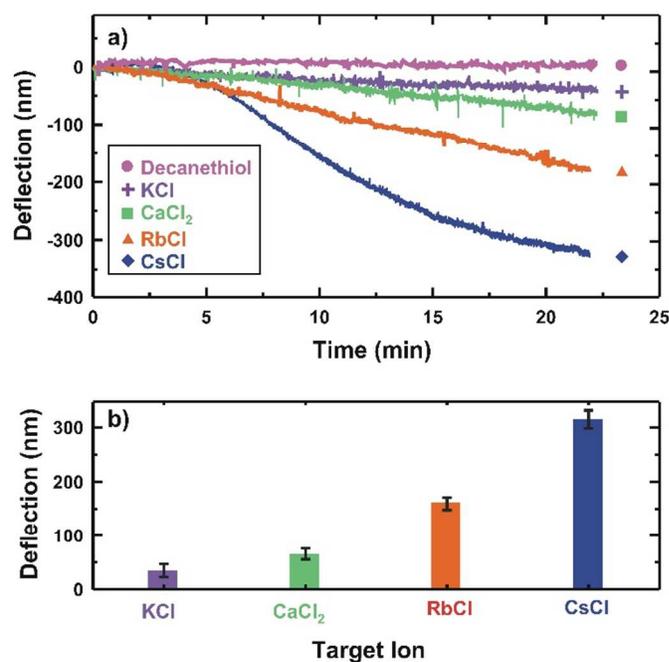
for  $\text{Cs}^+$  which was significantly greater than the deflection seen for  $\text{K}^+$  similar to what was reported by Ji *et al.*, albeit that in their case their receptor was a benzo-crown-6 moiety. The deflection seen with  $\text{Rb}^+$  was smaller than with  $\text{Cs}^+$  but greater than  $\text{K}^+$ . In addition, in our case only a relatively weak response was seen to  $\text{CaCl}_2$  which in our previous work with calix **1** showed the highest deflections to the MCLs. This latter result is not surprising as it is well-known in the literature that crown ethers are highly selective towards particular metal cations. In order to clearly demonstrate the repeatability of results obtained for different target ions, the average microcantilever deflection for three experiments of each concentration was calculated and shown in Fig. 4b. Each error bar corresponds to the standard deviation obtained from three separate experiments. This figure shows the excellent reproducibility obtained from our system.



**Fig 3:** STM images of calix[4]arene-crown-5 compound **3** which forms a self-assembled monolayer on the gold surface.

Previously, Zhang and Echegoyan<sup>3d</sup> reported the synthesis and metal ion cation recognition properties using SAMs of their *cone* and *1,3-alternate* bis-thioctic ester derivatives of *p-tert*-butylcalix[4]crown-6 on gold-coated electrodes. In contrast to our findings with **3** these authors showed that their *cone* regioisomer did not show any binding to  $\text{Cs}^+$  and that only the corresponding *1,3-alternate* did. However, it should be noted that besides having a "crown-6" functionality, their thioctic acid ester functionalities which are linked to the other *distal* 1,3-lower rim oxygens via triethyleneglycol tethers are much longer than the tether of the thioacetate in **3**. Thus, since the sulfur atoms in **3** are situated at a shorter distance away from the

lower-rim oxygens than the furthestmost atoms of the "crown-5" group, in order to account for our STM observation there are two possibilities: (a) only one sulfur in each molecule of **3** is attached to the Au surface, or (b) despite the evidence that **3** is in a *cone* conformation, it cannot be ruled out that a conversion to the *1,3-alternate* atropisomer occurs upon formation of the SAM onto the Au. In either case, the  $\text{Cs}^+$  as well as the  $\text{Rb}^+$  binding could be accommodated within the "crown" but with the *1,3-alternate* conformer being the more favourable for the binding as was seen by Zhang and Echegoyan<sup>3d</sup> in their case. However, as suggested by one of the referees, should the crown be in a "puckered"-type conformation<sup>17</sup> in the case of (a) above, it could "cap"  $\text{Rb}^+$  or  $\text{Cs}^+$  from one side of the coordination sphere. This would result in the relatively smaller sensitivity difference seen for these two cations (Fig. 4b). Alternatively, these large cations could be instead be more favourably accommodated within the cavity formed by the calixarene phenyl groups instead of the "crown-5" as a result of favourable  $\pi$ -cation interactions.<sup>18</sup>



**Fig 4:** (a) The response of microcantilever sensor functionalized with calixarene-crown-5 compound **3** to the introduction of different target ions. (b) The microcantilever deflection plotted as a function of the different target ion. Each data point represents to the average microcantilever deflection obtained from three experiments with the corresponding standard deviation shown by error bars.

## Conclusions

The synthesis of the "bimodal" or upper- and lower-rim functionalized calix-crown-5 **3** reported herein unexpectedly formed preferentially in a *cone* conformation. This was confirmed both by NMR spectroscopy and by a single-crystal X-ray crystallography. As with an earlier bimodal calixarene **1** previously reported by our group, the thioacetate functionalities

in **3** enabled it to form stable SAMs onto the Au surface of a MCL, albeit that in the case of **3** there were only two such groups compared with the four groups in **1**. The exact mode of binding of the thioacetate groups to Au has not been confirmed unequivocally but it has been suggested by others<sup>15</sup> to occur via extrusion of the acetate group and a direct sulphur-Au bond formation. Regardless, the strong MCL response to aqueous Ca<sup>2+</sup> in **1** was not seen with **3** which, instead, showed sensitivity to aqueous Cs<sup>+</sup> and to a lesser extent Rb<sup>+</sup> ions and negligible response to K<sup>+</sup>. This selectivity suggests that a suite of similar bimodally-functionalized calixarenes can be tailor-made to respond to a mixture of metal cations with a multi-MCL device in which several MCLs with suitable reference MCLs can be developed, a goal which we are striving to achieve.

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### Notes and references

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† Electronic Supplementary Information (ESI) available: <sup>1</sup>H-, <sup>13</sup>C-NMRT and MS data for compounds **3** and **6**. CCDC 1013564 (**3**). For crystallographic data in CIF or other electronic format see DOI:10.1039/b000000x/

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- Crystal Data for **3** (acetonitrile:ethanol): C<sub>62</sub>H<sub>88</sub>O<sub>6</sub>S<sub>2</sub> (M=1041.44 g/mol): monoclinic, space group P2<sub>1</sub>/n (no. 14), a= 21.9907(9)Å, b= 27.7429(14)Å, c= 29.1299(12)Å, β= 95.471(3), V= 17690.8(14) Å<sup>3</sup>, Z=12, T= 296.15K, μ(CuKα) = 1.242 mm<sup>-1</sup>, Dcalc= 1.173 g/cm<sup>3</sup>, 236792 reflections measured (4.82 ≤ 2θ ≤ 95.672), 16373 unique (R<sub>int</sub>= 0.1965, R<sub>sigma</sub>= 0.1372) which were used in all calculations. The final R<sub>1</sub> was 0.1519 (I > 2σ(I)) and wR<sub>2</sub> was 0.4584 (all data). CCDC 1013564†. See figures A-C in the SI.
- For theoretical and other recent studies into the nature of SAM and sulfur-Au bonds see (a) S. Miranda-Rojas, A. Munoz-Castro, R. Arratia-Perez and F. Mendizabal, *Phys. Chem. Chem. Phys.*, 2013, **15**, 20363-20370. (b) J. A. Fischer, V. C. Zoldan, G. Beitez, A. A. Rubert, E. A. Ramirez, P. Carro, R. C. Salvezza, A. A. Pasa and M. E. Vela, *Langmuir*, 2012, **28**, 15278-15285. (c) H. Häkkinen, *Nature Chem.* 2012, **4**, 443-455.
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- A detailed DFT computational study is currently on-going and will be reported on in due course.