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Design and Synthesis of a New Class of Twin-Chain Amphiphiles for Self-Assembled Monolayer-based Electrochemical Biosensor Applications

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Abstract

A new class of twin-chain hydroxyalkylthiols (mercaptoalkanols) featuring a nearly constant cross-section and the potential for modification of one or both termini are available with complete regioselectivity through Pd-mediated couplings of benzene diiododitriflate, including an example of a previously unreported coupling to generate an ortho-substituted arene bis acetic acid. Self-assembled monolayers (SAMs) prepared from the new amphiphiles demonstrate improved stability in an electrochemical sensor system compared with monolayers prepared from analogous single chain thiols.

Keywords

amphiphile; multivalent; self-assembled monolayer; thiol; cross-coupling; sensor

Introduction

The use of functionalized amphiphiles is central to a wide array of applications and disciplines.^[1–3] One of the most important classes of amphiphiles is based upon long-chain thiols. The strength of the gold-sulfur interaction, combined with the selectivity of gold for thiols and related functional groups, provides the basis for creation of a robust self-assembled monolayers (SAMs) which can tolerate a diverse array of functionality (commonly, –OH, –N₃, or –CH₃) at the terminus, or “tail” of the amphiphile.^[4] When incorporated in SAM-based electrochemical biosensors, these functionalized amphiphiles serve to passivate and provide stability to the sensing element and/or to tether the sensing element to the surface. The stability of the SAM, and therefore of the sensor, increases with the chain length of the thiol component.^[5] However, in electrochemical biosensor applications, the use of very long chain thiol backbones would result in the formation of highly resistive monolayers consequently impeding electrochemical read-outs. To address this, we now report the synthesis of a new class of arene-crosslinked twin-chain dithiol amphiphiles. The new amphiphiles, which feature a nearly constant cross-section and functionalized termini, form stable SAM-based sensors more capable of withstanding multiple electrochemical perturbations compared to single-chain amphiphiles of similar length.

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The vast majority of amphiphiles utilized for surface passivation or substrate attachment in gold-thiolate biosensors are single-chain mercaptoalkanols (hydroxyalkylthiols),^[6] the limitations of which have been discussed elsewhere.^[7] A number of multidentate thiol-based amphiphiles have also been reported (Figure 1). Amphiphiles based upon multidentate thiols have several advantages over their single-chain counterparts; they absorb more rapidly onto the gold surface and they generate more stable SAMs.^[8, 9] These properties are directly relevant to the performance, stability, and reusability of biosensors. However, existing multidentate thiols either possess unfunctionalized termini, limiting the ability to create functional monolayers; or else feature a significant mismatch between the multivalent “head” and the termini.^[10,11,12] As part of a collaboration targeting creation of SAM-based sensors on nanomaterial surfaces, we became interested in multivalent amphiphiles incorporating functionalized termini and maintaining a nearly constant cross-section down the long axis. Herein, we report the synthesis of a new class of twin-chain thiols, which, upon incorporation in electrochemical biosensors, result in SAMs possessing improved stability compared those prepared from an analogous single-chain thiol

Results and Discussion

Our initial investigations focused on amphiphiles **1** and **2**, which were chosen for comparability to 13- and 11-carbon single-chain thiol amphiphiles, respectively. The key steps in the construction of the molecular frameworks were anticipated to be sequential cross-coupling reactions of diiododitriflate **3** (Scheme 1). Synthesis of the C₁₃ twin-chain amphiphile **1** was based upon research from our lab demonstrating the ability to prepare 1,2,4,5-tetralkynylarenes from **3** with complete regiochemical control through two-fold Sonogashira reactions.^[13] The synthesis of the shorter C₁₁ amphiphile **2** would require a new approach in which the two chains comprising the terminus would be introduced via two-fold cross-coupling of bistriflate with a silyl ketene acetal.

The synthesis of **1** commenced with the two-fold Sonogashira cross-coupling of **3** with the benzyl ether of 4-pentyn-1-ol (Scheme 2). Subsequent coupling of the resulting dialkynylditriflate **4** with the benzoyl ester of 4-pentyn-1-ol generated tetraalkyne **5**. We had originally planned to employ Pd-catalyzed reaction with H₂ to achieve saturation of all four alkynes and hydrogenolytic deprotection of both benzyl ethers. However, reaction at room temperature and atmospheric pressure delivered a mixture of partially saturated products.^[14] Reaction at 40 °C and 2 atm pressure furnished a modest yield (40%, not shown) of diol **6**, accompanied by byproducts which were saturated but retained one (30%) or both (10%) of the benzyl ethers. Although the overall yield could be improved by resubjecting the isolated byproducts to the reaction conditions, we found that complete saturation and deprotection of **5** could be easily achieved in high yield by tandem application of Raney nickel (Raney Ni) and Pd/H₂. The alcohols of **6** were activated as methanesulfonates, which were displaced with KSac to provide the bisthioester in 74% yield over two steps. Reduction with DIBAL-H removed both the benzoate and thioacetate protecting groups to provide the C₁₃ twin-chain amphiphile (**1**).

The synthesis of the C₁₁ amphiphile **2**, illustrated in Scheme 3, also began with a two-fold Sonogashira coupling of **3**. The product, dialkynylditriflate **7**, was subjected to a Pd-mediated coupling with silyl ketene acetal **8** to provide bisester **9** in moderate yield. Although the coupling of silyl ketene acetals with iodoarenes or aryl triflates has been described, ours is the first example of application to *ortho* bisfunctionalization.^[15] The ketene acetal couplings proved considerably more challenging than the Sonogashira reactions described earlier. Attaining even moderate yields of the two-fold coupling product (**9**) required the use of dry lithium acetate and relatively pure silyl ketene acetal; the latter was frequently contaminated with the *C*-silylated isomer, ethyl 2-trimethylsilylacetate.^[16,17]

However, even after reaction optimization, the monocarboxyethyl/monotriflate derived from a single cross-coupling was often observed as a major byproduct.^[18]

The monotriflate byproduct readily undergoes Sonagashira coupling with simple alkynes (not shown), suggesting a potentially general pathway for introduction of differentially functionalized termini onto future generations of twin-chain amphiphiles. In marked contrast to what we had observed for the tetraalkynylarenes, the bisalkynes are easily saturated using Pd/C and hydrogen to furnish a nearly quantitative yield of the diol **10**, reflecting concomitant desilylation under the protic reaction conditions.^[19] Conversion of **10** to the corresponding diol/dithiol **2** was achieved in good yield as for the C₁₃ substrate above. No oxidative degradation of the thiols was observed during the reaction, workup, or purification process. The twin-chain amphiphiles **1** and **2** are easily handled oils and are stable indefinitely when stored cold in the absence of light and oxygen.

Electrochemical DNA sensor

The synthesized amphiphiles were applied to the fabrication of a folding based electrochemical DNA (E-DNA) sensor. An electrochemically-cleaned gold disc electrode was immersed for 10 minutes in a 2 mM ethanolic solution of either **1**, **2**, or 11-hydroxyundecanethiol. The resulting SAMs were further modified (drop casting, 3 h) with a stem-loop DNA sensing element thiolated at the 5'-terminus and modified with methylene blue (MB) at the 3'-terminus.^[20] The fabricated sensors were then rinsed with DI water and placed in an electrochemical cell where the stability of the sensors was assessed by monitoring the MB current using alternating current voltammetry, (ACV) scanning every 12 hours over a period of 72 hours (Fig. 2). Whereas the sensor prepared with the single chain amphiphile exhibited significant loss of response after 24–36 h, the sensors fabricated with **1** and **2** retained nearly 100% of the original response after 72 h, highlighting the stability of the SAMs derived from the twin-chain amphiphiles.

As a final test of stability, the sensors recovered from the ACV monitoring after 72 h (see above) were challenged/hybridized with 1.0 μ M complete complementary target DNA to which all the sensors responded. Upon sensor regeneration with deionized water, the MB signal was also regenerated as would be expected for this class of sensors (Fig. 3).^[20]

Conclusions

A new class of twin-chain amphiphiles has been prepared using routes which should be easily adaptable to a range of backbones and functional groups. The hydroxyl groups of the new amphiphiles, while applied here as part of a wettable passivating layer, provide the foundation for synthesis of functionalized nanomaterials allowing control of nearest neighbour interactions at the surface of the monolayer.

In initial tests, sensors fabricated using the new amphiphiles showed improved stability compared to those prepared from a single chain thiol. Although the terminal hydroxyl groups of the amphiphiles Electrochemical characterization of SAMs derived from **1** and **2**, along with details of the performance of E-DNA sensors fabricated from these amphiphiles, will be reported separately.

Experimental Section

General Information

All reactions were carried out in flame dried glassware under an atmosphere of dry nitrogen with magnetic stirring. Solvents were used as purchased with the exception of THF and CH₂Cl₂, which were distilled from Na/Ph₂CO and CaH₂, respectively. Thin layer

chromatography (TLC) was performed on 0.25 mm hard-layer silica G plates; developed plates were visualized with UV lamp and/or by staining: 1% aq. KMnO_4 (for unsaturated compounds); I_2 (general); or vanillin or phosphomolybdic acid (general, after charring). NMR spectra were obtained in CDCl_3 . ^1H NMR spectra are reported as δ in ppm, (multiplicity, integration, coupling constant(s) in Hz). ^{13}C NMR spectra are reported as δ in ppm. Both ^1H and ^{13}C spectra are referenced to residual CDCl_3 . Infrared spectra were recorded as neat ATR films with selected absorbances reported in wavenumbers (cm^{-1}). HRMS analysis was obtained with the ionization source as listed for each compound. Melting points are uncorrected.

Abbreviations: RBF = round bottom flask; EtOAc = ethyl acetate; Hex = hexane; DMAP = *N,N'*-dimethylaminopyridine.

1,2-Diiodo-4,5-dimethoxybenzene:^[13,21]—To a flame-dried 100 mL RBF equipped with a short air condenser was added H_5IO_6 (0.41 equiv, 25.6 mmol, 5.84 g) and methanol (36 mL). The mixture was stirred at r.t., then I_2 (0.8 equiv, 50.2 mmol, 12.76 g) was added. The reaction was stirred vigorously for 10 min, after which 1,2-dimethoxybenzene (1 equiv, 63 mmol, 8.7 g, 8.0 mL) was added in one portion via syringe. The reaction was heated to 70 °C in an oil bath for 5 h, resulting in the formation of a white solid which made stirring difficult; however, the reaction proceeded even without efficient stirring. The hot solution was poured into dilute aqueous $\text{Na}_2\text{S}_2\text{O}_5$ (~100 mL) and the mixture was cooled to r.t. The solid collected by filtration through a glass frit was washed quickly with two 30 mL portions of cold MeOH and dried *in vacuo* to afford the diiodoarene (21.07 g, 54 mmol, 86%) as a white solid that was deemed pure by NMR and used without further purification. R_f = 0.49, 20% EtOAc/Hex. Mp = 134.5–136.0 °C. ^1H NMR (600 MHz): δ 7.25 (s, 2H), 3.85 (s, 6H). ^{13}C NMR (150 MHz): δ 149.6, 121.7, 96.1, 56.2.

1,2-Dihydroxy-4,5-diiodobenzene:^[13,22]—A flame-dried 250 mL RBF was charged with 1,2-diiodo-4,5-dimethoxybenzene (1 equiv, 10 mmol, 3.90 g) and then evacuated/backfilled with nitrogen (3 $\times$) before addition of CH_2Cl_2 (70 mL). The solution was cooled to 0 °C and BBr_3 (2.5 equiv, 25 mmol, 25 mL of a 1.0 M solution in CH_2Cl_2) was added via syringe pump over 20 min. The reaction was stirred at 0 °C for 4 h then quenched with H_2O (50 mL). The separated aqueous layer was extracted with Et_2O (2 $\times$ 75 mL). The combined organic layers were dried with MgSO_4 , filtered through a pad of silica, and concentrated *in vacuo* to afford the dihydroxy diiodobenzene (3.61 g, 9.99 mmol, quantitative) as an off-white solid that was deemed pure by NMR and used without further purification. R_f = 0.50, 50% EtOAc/Hex. Mp = 116.0–116.5 °C. ^1H NMR (400 MHz, acetone- d_6): δ 8.48 (bs, 2H), 7.38 (s, 2H). ^{13}C NMR (150 MHz, acetone- d_6): δ 146.5, 125.6, 93.7.

4,5-Diiodo-1,2-phenylene bistrifluoromethanesulfonate (3):^[13]—To a flame-dried 100 mL RBF was added 1,2-dihydroxy-4,5-diiodobenzene (1 equiv, 7.85 mmol, 2.84 g), CH_2Cl_2 (55 mL), and pyridine (5 equiv, 39 mmol, 3.10 g, 3.16 mL). The solution was cooled to 0 °C and TiF_4 (2.2 equiv, 17.3 mmol, 4.88 g, 2.91 mL) was added dropwise via syringe over 10 min. The reaction was stirred for 6 h while warming to ambient temperature, then cooled to 0 °C and quenched with H_2O (30 mL). The separated aqueous layer was extracted with CH_2Cl_2 (2 $\times$ 30 mL). The combined organic layers were dried with MgSO_4 and filtered through a tall pad of silica. The pad was washed carefully with CH_2Cl_2 to avoid the elution of impurities, and the filtrate was concentrated *in vacuo* to afford **3** (4.90 g, 7.82 mmol, quantitative) as an off-white solid that was deemed pure by NMR and used without further purification. (Note: For reaction runs in which small amounts of impurities were observed after filtration, the product could be obtained in pure form following column chromatography utilizing 10% EtOAc/Hex as the mobile phase.) R_f = 0.60, 10% EtOAc/

Hex. Mp = 46.5–47.7 °C. ^1H NMR (400 MHz): δ 7.91 (s, 2H). ^{13}C NMR (100 MHz): δ 139.6, 133.4, 118.5 (q, $J_{\text{C,F}} = 321.0$ Hz), 108.0. FTIR: 1429, 1335, 1215, 1125, 1105, 868, 788, 745, 689 cm^{-1} . HRMS-ESI: calc. for $\text{C}_8\text{H}_2\text{F}_6\text{I}_2\text{NaO}_6\text{S}_2$ ($\text{M}+\text{Na}$) $^+$: 648.7184; found: 648.7164.

5-Benzyloxypentyne:^[23]—To a flame dried 250 mL RBF was added NaH (2 equiv, 47.6 mmol, 1.9 g of a 60% dispersion in mineral oil). The solid was washed with hexanes (15 mL). THF (95 mL) was added and the suspension was cooled to 0 °C. Pentynol (1 equiv, 23.8 mmol, 2.0 g) was added dropwise in THF (5 mL). BnBr (0.92 equiv, 21.9 mmol, 2.60 mL) was added dropwise. The reaction was allowed to come to r.t. over 16 h and then quenched with sat. aq. NH_4Cl (25 mL). The mixture was diluted with H_2O (20 mL) and extracted with EtOAc (2×40 mL). The brine-washed (40 mL) organic layer was dried with Na_2SO_4 and concentrated *in vacuo*. Purification via flash chromatography (4% EtOAc/Hex) afforded the benzyl ether (3.60 g, 20.7 mmol, 94%) as a colorless liquid: $R_f = 0.41$, 5% EtOAc/Hex. ^1H NMR (300 MHz): δ 7.29–7.44 (5H), 4.55 (s, 2H), 3.61 (t, 2H, $J = 6.2$ Hz), 2.36 (td, 2H, $J = 7.1, 2.6$ Hz), 1.97 (t, 1H, $J = 2.6$ Hz), 1.81–1.93 (m, 2H). ^{13}C NMR (75 MHz): δ 138.5, 128.4, 127.63, 127.58, 84.0, 73.0, 68.7, 68.5, 28.7, 15.3. CAS: 57618-47-0.

4,5-Bis(5-benzyloxypent-1-yn-1-yl)-1,2-phenylene

bistrifluoromethanesulfonate (4):^[13]—A flame dried 20 mL vial fitted with a screw-cap septa was charged with $\text{PdCl}_2(\text{PPh}_3)_2$ (0.06 equiv, 0.12 mmol, 84 mg), CuI (0.12 equiv, 0.24 mmol, 45.6 mg), and 4-pentynol (1 equiv, 2 mmol, 1.25 g). The vessel was evacuated/backfilled with nitrogen ($3 \times$), after which were sequentially added THF (4 mL), Et_3N (3 equiv, 6 mmol, 0.85 mL), and 5-benzyloxypentyne (2.3 equiv, 4.6 mmol, 802 mg) in 1 mL THF. The reaction was stirred for 3 h at r.t., filtered through a pad of silica, which was washed with Et_2O , concentrated *in vacuo*, and purified via flash chromatography (step gradient Hex to 10% EtOAc/Hex) to afford **4** (1.14 g, 1.59 mmol, 79%). $R_f = 0.27$, 10% EtOAc/Hex. ^1H NMR (600 MHz): δ 7.42 (s, 2H), 7.27–7.39 (10H), 4.56 (s, 4H), 3.65 (t, 4H, $J = 6.0$ Hz), 2.62 (t, 4H, $J = 7.1$ Hz), 1.92–1.98 (m, 4H). ^{13}C NMR (150 MHz): δ 138.8, 138.3, 128.4, 128.2, 127.59, 127.56, 126.3, 121.7, 119.6, 117.5, 115.3, 98.1, 77.4, 73.0, 68.5, 28.6, 16.5. FTIR: 2859, 2230, 1489, 1433, 1210, 1178, 1135, 1080, 732 cm^{-1} . HRMS-ESI: calc. for $\text{C}_{32}\text{H}_{28}\text{F}_6\text{O}_8\text{S}_2\text{Na}$ ($\text{M}+\text{Na}$) $^+$: 741.1027; found: 741.1039.

5-Benzoyloxypentyne:^[24]—To a flame dried 100 mL RBF was added pentynol (1 equiv, 24 mmol, 2.0 g) and CH_2Cl_2 (80 mL). The reaction was cooled to 0 °C and BzCl (1.2 equiv, 28 mmol, 3.3 mL) was added dropwise, followed by DMAP (0.1 equiv, 2.4 mmol, 300 mg), and Et_3N (7 mL). The reaction was allowed to come to r.t. over 12 h, and then quenched with 2 N HCl (10 mL). The EtOAc extract (2×40 mL) was washed with brine (40 mL) and dried with Na_2SO_4 . The residue obtained upon concentration *in vacuo* was purified via flash chromatography (2.5% EtOAc/Hex) to afford the protected alkynol (4.02 g, 21.4 mmol, 89%) as a colorless oil. $R_f = 0.57$, 10% EtOAc/Hex. ^1H NMR (600 MHz): δ 8.03–8.07 (2H), 7.53–7.60 (1H), 7.42–7.48 (2H), 4.44 (t, 2H, $J = 6.1$ Hz), 2.40 (td, 2H, $J = 7.3, 2.7$ Hz), 1.98–2.05 (overlapping signals, 3H). ^{13}C NMR (150 MHz): δ 166.5, 132.9, 130.3, 129.6, 128.3, 83.0, 69.1, 63.4, 27.7, 15.4. CAS: 5390-04-5.

4,5-Bis(5-benzyloxypent-1-yn-1-yl)-1,2-phenylene-bis(pent-4-yne-1-ol-5-yl,

benzoate ester) (5)—A flame dried 20 mL vial fitted with a screw-cap septa was charged with $\text{PdCl}_2(\text{PPh}_3)_2$ (0.12 equiv, 0.18 mmol, 127 mg), CuI (0.30 equiv, 0.45 mmol, 89.4 mg), and Bu_4NI (3 equiv, 4.5 mmol, 1.65 g). The vessel was evacuated/backfilled with nitrogen $3 \times$ and the solution was allowed to stir for 5 min at r.t, followed by the addition of bistriflate **4** in a 5:1 mixture of DMF/ Et_3N (7 mL). The mixture was stirred for 5 min at r.t., and 5-benzoyloxypentyne (4.1 equiv, 6.1 mmol, 980 mg) was then added in 1.5 mL of 5:1 DMF/

Et₃N. The reaction was heated to 70 °C (oil bath) for 5.5 h and then cooled to r.t. The crude reaction mixture was filtered through a pad of silica, which was washed with Et₂O. The filtrate was concentrated *in vacuo*, and the residue purified via flash chromatography (15% EtOAc/Hex) to afford **5** (930 mg, 1.17 mmol, 79%) as a colorless oil. *R*_f = 0.39, 20% EtOAc/Hex. ¹H NMR (600 MHz): δ 8.04–8.10 (4H), 7.54–7.60 (2H), 7.42–7.47 (4H), 7.39–7.41 (2H), 7.33–7.38 (8H), 7.27–7.31 (2H), 4.55 (s, 4H), 4.53 (t, 4H, *J* = 6.3 Hz), 3.66 (t, 4H, *J* = 6.2 Hz), 2.70 (t, 4H, *J* = 7.0 Hz), 2.60 (t, 4H, *J* = 7.0 Hz), 2.11 (quint, 4H, 6.6 Hz), 1.94 (quint., 4H, *J* = 6.6 Hz). ¹³C NMR (150 MHz): δ 166.5, 138.5, 135.3, 133.0, 130.2, 129.6, 128.38, 128.36, 127.60, 127.56, 125.3, 124.9, 95.0, 93.9, 79.6, 79.1, 73.0, 68.7, 63.7, 28.9, 28.0, 16.7, 16.6. FTIR: 3675, 2988, 2972, 2901, 2229, 1716, 1451, 1394, 1269, 1107, 1068, 1027, 900 cm⁻¹. HRMS-ESI: calc. for C₅₄H₅₀O₆Na (M+Na)⁺: 817.3505; found: 817.3503. Note: This procedure differs from a previous report in the use of 12 mol% PdCl₂(PPh₃)₂ rather than 6 mol%.^[13]

1,2-Bis(5-benzoyloxypentyl)-4,5-bis(5-hydroxypentyl)benzene (6)—Raney Ni (120 mg, 50% in water) was added to an 8 mL vial. The solid was collected on a stir bar and washed with MeOH (3 × 5 mL). The vial was then fitted with a screw-cap septa and charged with a solution of **5** (1 equiv, 0.25 mmol, 199 mg) in 4 mL of 3:1 MeOH/EtOAc. The vial was placed under an atm of H₂ (balloon) and the reaction was stirred for 16 h. The reaction mixture was filtered through a silica plug and the filtrate was concentrated under vacuum. The residue was taken up in 3 mL THF and added to an 8 mL vial which had been charged with 20 mg of 10 wt% Pd/C. The reaction was placed under an atm of H₂ for 16 h and then filtered through a silica plug. The filtrate was concentrated *in vacuo*, and purified via flash chromatography (55% EtOAc/Hex) to afford **6** (129 mg, 0.21 mmol, 82%) as a colorless oil. *R*_f = 0.30, 60% EtOAc/Hex. ¹H NMR (600 MHz): δ 8.04–8.10 (4H), 7.54–7.61 (2H), 7.42–7.50 (4H), 6.94 (s, 2H), 4.36 (t, 4H, *J* = 6.7 Hz), 3.67 (t, 4H, *J* = 6.6 Hz), 2.53–2.68 (8H), 1.80–1.91 (6H), 1.53–1.72 (16H), 1.44–1.51 (4H). ¹³C NMR (150 MHz): δ 166.7, 137.6, 137.3, 132.8, 130.4, 129.9, 129.5, 128.3, 65.0, 62.7, 32.5, 32.21, 32.15, 31.2, 30.9, 28.6, 26.1, 25.8. FTIR: 3776, 2988, 2972, 2901, 1717, 1334, 1271, 1067, 1057, 1028 cm⁻¹. HRMS-ESI: calc. for C₄₀H₅₄O₆Na (M+Na)⁺: 653.3818; found: 653.3823.

1,2-Bis(5-benzoyloxypentyl)-4,5-bis(5-methansulfonylpentyl) benzene—To a flamed-dried 20 mL vial fitted with a screw-cap septa was added **6** (1 equiv, 0.34 mmol, 215 mg), CH₂Cl₂ (4 mL), and Et₃N (4 equiv, 1.36 mmol, 0.19 mL). DMAP (0.1 equiv, 0.034 mmol, 4.2 mg) was added followed by the dropwise addition of MsCl (3 equiv, 1.02 mmol, 0.08 mL). The reaction was stirred for 3 h and quenched with sat. aq. NaHCO₃ (10 mL). The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (3 × 10 mL). The combined organic layers were washed with H₂O (20 mL), dried with Na₂SO₄, concentrated *in vacuo*, and purified via flash chromatography (45% EtOAc/Hex) to afford the bismethanesulfonate (294 mg, 0.37 mmol, 91%) as a colorless oil. *R*_f = 0.27, 40% EtOAc/Hex. ¹H NMR (600 MHz): δ 8.01–8.11 (4H), 7.54–7.62 (2H), 7.46 (t, 4H, *J* = 7.6), 6.92 (s, 2H), 4.35 (t, 4H, *J* = 6.6 Hz), 4.26 (t, 4H, *J* = 6.6 Hz), 3.02 (s, 6H), 2.60 (bt, 4H, *J* = 8.0 Hz), 2.57 (bt, 4H, *J* = 8.0), 1.77–1.88 (8H), 1.48–1.70 (16H). ¹³C NMR (150 MHz): δ 166.7, 137.6, 137.3, 132.9, 130.5, 129.9, 129.5, 128.3, 70.1, 65.0, 37.4, 32.2, 32.1, 31.1, 30.8, 29.1, 28.7, 26.2, 25.6. FTIR: 2937, 1714, 1352, 1272, 1173, 1114, 1070, 944, 908 cm⁻¹. HRMS-ESI: calc. for C₄₂H₅₈O₁₀S₂Na (M+Na)⁺: 809.3369; found: 809.3367.

1,2-Bis(5-benzoyloxypentyl)-4,5-bis(5-(acetylthiyl)pentyl) benzene—To a flame dried 8 mL vial fitted with screw-cap septa was added the bis methanesulfonate (1 equiv, 0.282 mmol, 222 mg) and DMF (2.5 mL), followed by KSAc (3 equiv, 0.85 mmol, 97 mg). The reaction was stirred for 14 h and then diluted with Et₂O (20 mL) and H₂O (10 mL). The layers were separated and the organic layer was washed with sat. aq. NaHCO₃ (3 × 10 mL),

dried with Na₂SO₄, concentrated *in vacuo*, and purified via flash chromatography (10% EtOAc/Hex) to afford the bis thioacetate (170 mg, 0.228 mmol, 81%) as a colorless oil. R_f = 0.32, 15% EtOAc/Hex. ¹H NMR (600 MHz): δ 8.07 (d, 4H, J = 7.3 Hz), 7.58 (t, 2H, J = 7.4 Hz), 7.46 (t, 4H, J = 7.8 Hz), 6.92 (s, 2H), 4.36 (t, 4H, J = 6.7 Hz), 2.90 (t, 4H, J = 7.3 Hz), 2.60 (bt, 4H, J = 7.9 Hz), 2.55 (bt, 4H, J = 7.9 Hz), 2.35 (s, 6H), 1.80–1.89 (8H), 1.54–1.70 (8H), 1.44–1.51(4H). ¹³C NMR (150 MHz): δ 195.9, 166.7, 137.5, 137.3, 132.8, 130.5, 129.9, 129.5, 128.3, 65.0, 32.3, 32.2, 31.1, 30.9, 30.7, 29.5, 29.1, 28.7, 26.3. FTIR: 3684, 3675, 2988, 2972, 2901, 1717, 1688, 1406, 1394, 1383, 1230, 1057, 1028 cm⁻¹. HRMS-ESI: calc. for C₄₄H₅₈O₆S₂Na (M+Na)⁺: 769.3573; found: 769.3568.

1,2-Bis(5-hydroxypentyl)-4,5-bis(5-thiylpentyl)benzene (1)—A flame dried 8 mL vial fitted with a screw-top cap was charged with the bithioacetate (1 equiv, 0.193 mmol, 144 mg) and THF (2.5 mL). *i*-Bu₂AlH (DIBAL-H) (12 equiv, 2.3 mmol, 1.55 mL of a nominally 1.5 M solution in toluene) was added dropwise. The reaction was stirred at r.t. for 2.5 h, cooled to 0 °C, and quenched by the careful addition of 2N HCl (4 mL). The solution was diluted with H₂O (10 mL) and extracted with Et₂O (3 × 10 mL). The organic layers were washed with brine (10 mL) and dried with Na₂SO₄. The residue obtained upon concentrated *in vacuo* was purified via flash chromatography (50% EtOAc/Hex) to afford **1** (74 mg, 0.163 mmol, 84%) of a colorless oil. R_f = 0.19, 45% EtOAc/Hex. ¹H NMR (600 MHz): δ 6.92 (s, 2H), 3.68 (t, 4H, 6.6 Hz), 2.53–2.61 (12H), 1.56–1.72 (18H), 1.45–1.53 (8H), 1.37 (t, 2H, J = 7.9 Hz). ¹³C NMR (150 MHz): δ 137.6, 137.4, 129.9, 62.9, 33.9, 32.6, 32.3, 32.2, 31.2, 30.8, 28.5, 25.9, 24.6. FTIR: 3353, 2930, 2857, 2358, 2338, 1775, 1460, 1143 cm⁻¹. HRMS-ESI: calc. for C₂₆H₄₆O₂S₂Na (M+Na)⁺: 477.2837; found: 477.2821.

6-(tert-Butyldimethylsilyloxy)hexyne:[25]—A flame dried 100 mL RBF was charged with hexynol (1 equiv, 25.5 mmol, 2.50 g), CH₂Cl₂ (60 mL), TBSCl (1.1 equiv, 28.1 mmol, 4.23 g), and imidazole (2.2 equiv, 56.1 mmol, 3.82 g). The reaction was stirred for 1.5 h, and then quenched with 40 mL sat. aq. NaHCO₃. The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (2 × 20 mL). The combined organic layers were dried with Na₂SO₄, concentrated *in vacuo*, and filtered through a pad of silica to afford the silyl-protected alkynol (4.93 g, 23.2 mmol, 91%) as a colorless oil. R_f = 0.70, 5% EtOAc/Hex. ¹H NMR (400 MHz): δ 3.65 (t, 2 H, J = 6.0 Hz), 2.24 (td, 2 H, J = 6.8, 2.7 Hz), 1.96 (t, 1 H, J = 2.5 Hz), 1.56–1.70 (2 H), 0.92 (s, 9 H), 0.07 (s, 6 H). ¹³C NMR (100 MHz): δ 84.5, 68.2, 62.6, 31.8, 25.9, 25.0, 18.3, 18.2, -5.3. CAS: 73448-13-2.

4,5-Bis[6-(tert-butyldimethylsilyloxy)hex-1-ynyl]-1,2-phenylene bis(trifluoromethanesulfonate) (7)—A flame dried 20 mL vial fitted with a screw-cap septa was charged with PdCl₂(PPh₃)₂ (0.06 equiv, 0.18 mmol, 126 mg), CuI (0.12 equiv, 0.36 mmol, 68 mg), and **3** (1 equiv, 3 mmol, 1.88 g). The vessel was evacuated/backfilled with nitrogen 3 ×, after which were sequentially added THF (5 mL), Et₃N (3 equiv, 9 mmol, 1.29 mL), and 6-(tert-Butyldimethylsilyloxy)hexyne (2.3 equiv, 6.9 mmol, 1.46 g; as a solution in 2.5 mL THF). The reaction was stirred for 3 h at r.t. and then filtered through a pad of silica, which was washed with Et₂O. The filtrate was concentrated *in vacuo* and the residue was purified via flash chromatography (step gradient, 0 to 2% EtOAc/Hex) to afford **7** (2.29 g, 2.29 mmol, 96%) as a colorless oil. R_f = 0.27, 2.5 % EtOAc/Hex. ¹H NMR (400 MHz): δ 7.44 (s, 2 H), 3.66–3.72 (4 H), 2.49–2.61 (4 H), 1.66–1.77 (8 H), 0.92 (s, 18 H), 0.08 (s, 12 H). ¹³C NMR (150 MHz): δ 138.8, 128.3, 126.3, 118.5 (q, $J_{C,F}$ = 320.9 Hz), 98.6, 77.3, 62.5, 31.9, 25.9, 24.9, 19.4, 18.3, -5.3. FTIR: 2945, 2930, 2858, 2230, 1489, 1436, 11247, 1211, 1179, 1137, 1087, 834, 807, 774 cm⁻¹. HRMS (ESI): calcd. for C₃₂H₄₈F₆O₈S₂Na [M + Na]⁺ 817.2131; found 817.2120.

((1-Ethoxyvinyl)oxy)trimethylsilane (8):^[26]—To a flame-dried 250 mL RBF was added $i\text{Pr}_2\text{NH}$ (1.2 equiv, 34.1 mmol, 4.8 mL) and THF (33 mL). The solution was cooled to 0 °C, and BuLi (1.1 equiv, 31.2 mmol, 19.5 mL of a nominally 1.6 M solution in Hexane) was added dropwise. The mixture was stirred for 15 min and then cooled to –78 °C. A mixture of EtOAc (1 equiv, 28.4 mmol, 2.8 mL) and TMSCl (1.2 equiv, 34.3 mmol, 4.4 mL) in THF (15 mL) was added over 5 min and the cooling bath was removed. The reaction was allowed to warm to r.t. and stirred for 4 h, after which solvent was removed *in vacuo*. The residue is taken up in 50 mL of Hex and filtered through a pad of Celite, which was washed with two 15 mL portions of Hex. Concentration *in vacuo* followed by distillation (70–80 °C, 40–50 torr) provided **8** as a colorless liquid (see NMR for approx. composition). CAS: 18295-66-4.

4,5-Bis[6-((tert-butyldimethylsilyl)oxy)hex-1-ynyl]-1,2-phenylene

bis(trifluoromethanesulfonate) (9)—A flame-dried 8 mL vial fitted with a screw-top septa cap was charged with $\text{Pd}(\text{PPh}_3)_4$ (0.15 equiv, 0.075 mmol, 87 mg) and anhydrous LiOAc (4 equiv, 2 mmol, 133 mg). The vessel was evacuated and backfilled with dry N_2 three times, followed by the addition of **7** (1 equiv, 0.5 mmol, 398 mg) and **8** (4 equiv (based on mass, ca. 75% purity by ^1H NMR), 2 mmol, 321 mg) in 3.5 mL THF. The sealed reaction vessel was placed in a 70 °C oil bath for 5 h and then cooled to r.t. before dilution with 10 mL H_2O and 10 mL EtOAc. The separated aqueous layer was extracted with EtOAc (2 $\times$ 10 mL) and the combined organic layers were washed with brine (1 $\times$ 20 mL) and dried with Na_2SO_4 . The residue obtained upon concentrated *in vacuo* was purified *via* flash chromatography (8% EtOAc/Hex) to afford **9** (134 mg, 0.20 mmol, 40%) as a colorless oil. R_f = 0.30, 10% EtOAc/Hex. ^1H NMR (400 MHz): δ 7.28 (s, 2H), 4.14 (q, 4H, J = 7.1 Hz), 3.68 (t, 4H, J = 5.8 Hz), 3.64 (s, 4H), 2.49 (t, 4H, J = 6.5 Hz), 1.64–1.78 (8H), 1.25 (t, 6H, J = 7.1 Hz), 0.92 (s, 18H), 0.07 (s, 12H). ^{13}C NMR (150 MHz): δ 170.8, 134.1, 132.5, 125.5, 94.0, 79.3, 62.7, 61.0, 38.7, 31.9, 26.0, 25.2, 19.4, 18.4, 14.1, –5.3. FTIR: 2987, 2856, 1735, 1250, 1211, 1102, 1030, 833, 773 cm^{-1} . HRMS-ESI: calc. for $\text{C}_{38}\text{H}_{62}\text{O}_6\text{Si}_2\text{Na}$ ($\text{M}+\text{Na}$) $^+$: 693.3983; found: 693.3961.

Diethyl 2,2'-(4,5-bis(6-hydroxyhexyl)-1,2-phenylene)diacetate (10)—A flame-dried 20 mL vial fitted with a screw-cap septa was charged with 10% (w/w) Pd/C (10 mg), followed by the addition of a solution of **9** (1 equiv, 0.155 mmol, 103 mg) in 8 mL 1:1 MeOH:EtOAc. The reaction was placed under an atmosphere of H_2 (balloon) and stirred for 18 h. The solution obtained after filtration through a pad of Celite was concentrated *in vacuo* to provide **10** (66 mg, 0.149 mmol, 97%) as a colorless oil. R_f = 0.41, 75% EtOAc/Hex. ^1H NMR (600 MHz): δ 7.03 (s, 2H), 4.15 (q, 4H, J = 7.1 Hz), 3.63–3.70 (overlapping s/t, 8H), 2.54–2.62 (m, 4H), 1.55–1.64 (10H), 1.39–1.45 (8H), 1.27 (t, 6H, J = 7.1 Hz). ^{13}C NMR (150 MHz): δ 171.7, 139.6, 131.5, 130.4, 62.9, 60.8, 38.6, 32.7, 32.2, 31.0, 29.4, 25.6, 14.2. FTIR: 3346, 2930, 2856, 1729, 1367, 1256, 1155, 1027 cm^{-1} . HRMS-ESI: calc. for $\text{C}_{26}\text{H}_{42}\text{O}_6\text{Na}$ ($\text{M}+\text{Na}$) $^+$: 473.2879; found: 473.2888.

Diethyl 2,2'-(4,5-bis(6-((methylsulfonyl)oxy)hexyl)-1,2-phenylene)diacetate—

To a flamed-dried 8 mL vial fitted with a screw-cap septa were sequentially added **10** (1 equiv, 0.124 mmol, 55 mg), CH_2Cl_2 (1.5 mL), Et_3N (4 equiv, 0.5 mmol, 0.075 mL), and DMAP (0.1 equiv, 0.013 mmol, 1.6 mg), and MsCl (3 equiv, 0.372 mmol, 0.031 mL, dropwise). The reaction was stirred for 3 h, then quenched with sat. aq. NaHCO_3 (10 mL). The layers are separated and the aqueous layer was extracted with CH_2Cl_2 (3 $\times$ 10 mL). The combined organic layers were dried with Na_2SO_4 and the residue obtained upon concentration *in vacuo*, was purified *via* flash chromatography (55% EtOAc/Hex) to afford the bis methanesulfonate (64 mg, 0.105 mmol, 85%) as a colorless oil. R_f = 0.86, 75% EtOAc/Hex. ^1H NMR (400 MHz): δ 7.03 (s, 2H), 4.25 (t, 4H, J = 6.5 Hz), 4.15 (q, 4H, J =

7.1 Hz), 3.66 (s, 4H), 2.60 (s, 6H), 2.54–2.62 (m, 4H), 1.79 (4H), 1.55–1.65 (4H), 1.39–1.45 (8H), 1.27 (t, 6H, $J = 7.1$ Hz). ^{13}C NMR (150 MHz): δ 171.6, 139.3, 131.5, 130.5, 70.1, 60.8, 38.6, 37.4, 32.1, 30.9, 29.1, 25.4, 14.2. FTIR: 2935, 2860, 1729, 1349, 1332, 1170, 1028, 948, 914, 729 cm^{-1} . HRMS-ESI: calc. for $\text{C}_{28}\text{H}_{46}\text{O}_{10}\text{S}_2\text{Na}$ ($\text{M}+\text{Na}$) $^+$: 629.2430; found: 629.2459.

Diethyl 2,2'-(4,5-bis(6-(acetylthio)hexyl)-1,2-phenylene) diacetate—To a flamed-dried 8 mL vial fitted with a screw-cap septa was added diethyl 2,2'-(4,5-bis(6-(methylsulfonyl)oxy)hexyl)-1,2-phenylene)diacetate (1 equiv, 0.101 mmol, 61 mg) in 1.5 mL DMF, followed by KSAc (5 equiv, 0.505 mmol, 58 mg). The reaction was stirred for 14 h and then quenched with sat. aq. NaHCO_3 (5 mL). After the mixture was diluted with 20 mL Et_2O , the separated organic layer was washed with sat. aq. NaHCO_3 (2×5 mL) and dried with Na_2SO_4 . The residue obtained upon concentration *in vacuo*, was purified *via* flash chromatography (15% EtOAc/Hex) to afford the bis thioacetate (46 mg, 0.081 mmol, 80%) as a colorless oil. $R_f = 0.22$, 10% EtOAc/Hex. ^1H NMR (400 MHz): δ 7.02 (s, 2H), 4.15 (q, 4H, $J = 7.1$ Hz), 3.66 (s, 4H), 2.89 (t, 4H, 7.3 Hz), 2.52–2.60 (m, 4H), 2.35 (s, 6H), 1.52–1.64 (8H), 1.38–1.46 (8H), 1.27 (t, 6H, $J = 7.1$ Hz). ^{13}C NMR (150 MHz): δ 196.0, 171.6, 139.5, 131.5, 130.4, 60.8, 38.6, 32.2, 31.0, 30.6, 29.5, 29.2, 29.1, 28.7, 14.2. FTIR: 2927, 2855, 1732, 1688, 1254, 1133, 1029, 950 cm^{-1} . HRMS-ESI: calc. for $\text{C}_{30}\text{H}_{46}\text{O}_6\text{S}_2\text{Na}$ ($\text{M}+\text{Na}$) $^+$: 589.2634; found: 589.2651.

2,2'-(4,5-Bis(6-thiylhexyl)-1,2-phenylene)diethanol (2)—A flame-dried 8 mL vial fitted with a screw-cap septa was charged with the bis thioacetate (1 equiv, 0.078 mmol, 44 mg) and 1 mL THF, after which was dropwise added DIBAL-H (12 equiv, 0.93 mmol; 0.65 mL of a nominally 1.5 M solution in toluene). The reaction was stirred for 3 h and then quenched by slow dropwise addition of 2 N HCl (2 mL) at 0 °C. The mixture was diluted with 10 mL H_2O and extracted with Et_2O (3×10 mL). The combined organic layers were washed with brine (10 mL) and dried with Na_2SO_4 . The residue obtained upon concentration *in vacuo* was and purified *via* flash chromatography (70% EtOAc/Hex) to afford **2** (22 mg, 0.055 mmol, 71%) as a colorless oil. $R_f = 0.22$, 50% EtOAc/Hex. ^1H NMR (600 MHz): δ 6.98 (s, 2H), 3.85 (t, 4H, $J = 6.5$ Hz), 2.90 (t, 4H, $J = 6.7$ Hz), 2.52–2.60 (m, 8H), 2.12 (s, 2H), 1.65 (quint., 4H, $J = 7.2$ Hz), 1.58 (quint., 4H, $J = 7.5$ Hz), 1.38–1.49 (8H), 1.36 (t, 2H, $J = 7.5$ Hz). ^{13}C NMR (150 MHz): δ 138.8, 134.3, 130.8, 63.6, 35.3, 33.9, 32.2, 31.2, 29.2, 28.2, 24.6. FTIR: 3332, 2925, 2853, 1503, 1460, 1040 cm^{-1} . HRMS-ESI: calc. for $\text{C}_{22}\text{H}_{38}\text{O}_2\text{S}_2\text{Na}$ ($\text{M}+\text{Na}$) $^+$: 421.2211; found: 421.2212.

E-DNA sensor fabrication—Prior to SAM formation, gold disk electrodes (2-mm diameter, CHI, Instruments, Austin, TX) were electrochemically cleaned by cycling between –0.4 and 1.6 V vs. Ag/AgCl in 0.5 M sulfuric acid until the gold oxide formation region of the voltammograms displayed three distinct peaks and successive scans showed minimal to no change. The E-DNA sensors were fabricated in two steps: (1) The electrochemically-cleaned gold disc electrodes were immersed in 2 mM ethanolic solution of either **1**, **2** or 11-hydroxyundecaneundecanol for 10 minutes. The electrodes were then rinsed with deionized water and dried with N_2 . (2) A stem-loop DNA sensing element thiolated at the 5'-end and modified with methylene blue (MB) at the 3'-end (see representation of sensor construct below) was then dropcasted on the pre-formed SAMs for 3 hours.^[19] Electrochemical measurements were performed at room temperature (22 ± 1 °C) using a CHI 1040A Electrochemical Workstation (CH Instruments, Austin, TX). The modified electrodes were analyzed using alternating current voltammetry (ACV) at a frequency of 10 Hz and an amplitude of 25 mV. All voltammograms were recorded in a physiological buffer solution (Phys2) consisting of 20 mM Tris, 140 mM NaCl, 5 mM KCl, 1 mM MgCl_2 , and 1 mM CaCl_2 ; the solution was adjusted to pH 7.4 with hydrochloric acid. For sensor stability

monitoring, ACV scans were collected every 12 hours for a total of 72 hours. The sensors were then interrogated/hybridized with 1.0 μ M complete complementary target DNA (see sequence below) until no change in the MB current was observed. The sensors were then regenerated by continuous rinsing with deionized water for 30 seconds. The sensors were subsequently transferred to a fresh Phys2 buffer solution for electrochemical monitoring of the regenerated current.

K-ras probe sequence: 5' HS-(CH₂)₁₁-CCGTTACGCCACCAGCTCCAAACGG-C7-MB-3'

K-ras target sequence: 5'-TTGGAGCTGGTGGCGTA-3'

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Examples of multidentate thiol amphiphiles.

Figure 2.
Comparison of stability of E-DNA sensors formed from 11-hydroxyundecanethiol, **1**, and **2**.

Figure 3.

Hybridization curves obtained from sensors passivated with 11-hydroxyundecanethiol (red), 1 (purple) and 2 (green) in the presence of 1.0 μM target DNA in Phys2 buffer after the 72-hr stability run. *K-ras* probe sequence: 5' HS-(CH₂)₁₁-CCGTTACGCCACCAGCTCCAAACGG-C7-MB-3'. *K-ras* target sequence: 5'-TTGGAGCTGGTGGCGTA-3'

Scheme 1.
Retrosynthetic analysis for the 13- and 11-carbon amphiphiles.

Scheme 2.
Synthesis of amphiphile **1**.

Scheme 3.
Synthesis of amphiphile **2**.