Rapid Evaluation and Screening of Interfacial Reactions on Self-Assembled Monolayers

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This paper reports 16 chemical reactions for elaborating the structures of self-assembled monolayers (SAMs) of alkanethiolates on gold. This work takes advantage of matrix-assisted laser desorption/ionization and time-of-flight mass spectrometry (MALDI-TOF MS) to rapidly characterize the products and yields of reactions that occur with molecules attached to monolayers. The paper also describes a method for screening reaction conditions, wherein monolayers are treated with an array of reactants and mass spectrometry is used to identify those regions that undergo reactions to give new, and unanticipated, products in high yield. These examples serve to increase the collection of reactions that can be used to elaborate the structures, and therefore the properties, of self-assembled monolayers of alkanethiolates on gold and to introduce label-free methods for screening interfacial reactions.

Introduction

The introduction of self-assembled monolayers of alkanethiolates on gold in 1983 was significant because this advance soon offered wide flexibility in creating surfaces having well-defined structures.[1] The ability to tailor the molecular level structure, and therefore the properties, of a surface has proven significant to studies in a broad range of areas, including electron-transfer processes, biomolecular recognition, and micro/nanofabrication.[2,3] The availability of reactions that can be used to elaborate the structures of preformed monolayers (together with the use of terminally functionalized alkanethiols in the preparation of monolayers) has been central to these applications.[4,5] Yet, the development of interfacial reactions remains difficult, primarily owing to the challenges in characterizing the products and yields of conversions. In practice, the development of each new reaction requires data from several analytical methods to establish the presence and yield of the anticipated reaction. The modest pace of interfacial reaction development (approximately 30 interfacial reactions have been reported over the past 20 years (Table 1)) is evidence of the challenges associated with these efforts.

As noted above, the primary difficulty in developing chemistries for elaborating the structures of monolayers lies in the characterization of products. Organic reactions performed in solution can be analyzed rapidly with a variety of reliable and informative techniques, including NMR spectroscopy, mass spectrometry, infrared spectroscopy, and X-ray crystallography. When working with interfacial reactions, by contrast, the small amount of compound (a few picomoles per square millimeter) and the attachment of the molecules to a surface prevent the use of these common methods. Instead, a combination of spectroscopic and ultrahigh vacuum techniques are used, including IR spectroscopy, X-ray photoelectron spectroscopy, contact angle goniometry, ellipsometry, scanning tunneling microscopy, atomic force microscopy, cyclic voltammetry, and surface plasmon resonance spectroscopy.[3,6,10,29] These analytical methods are combined with control reactions (for example, verifying that condensation of a soluble amine with an immobilized carboxylic acid does not proceed in the absence of an activating reagent) to ultimately validate interfacial reactions.

The need for better-suited analytical techniques is particularly important for the characterization of products having multiple functional groups and for products resulting from a sequence of reactions. We recently demonstrated that matrix-assisted laser

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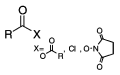
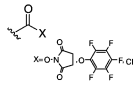
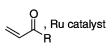
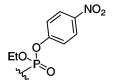
Table 1. Reactions That Have Been Performed on SAMs

SAM	Reagents	Product	Reference
			6-10
	$ClSO_2OH$		7
	$POCl_3$		7
	Ph−N=C=O		11,12
	DMTCl		10
	TFA		10
	$NaIO_4$		13
	$SOCl_2$		14
	ROH and EDC or di-*tert*-butyl carbodiimide		8,15-17
	NH_2R		6,14-19 10,20,21[a]
	X=C=N−R (X=S, O)		18,22 11,22[a]
	ROH		11
	H_2O		11
	−R		23,24[a]
	 Ru catalyst		25
	HSR		20,26[a]
	HSR		20,20[a]
	dithiothreitol		20
	*hv* and photoacid generator or TFA		27,28
	RNH_2		13,29-32
			27,33
			34,35
	H_2NR		36
	hv		37
	electrochemistry		33,38[a]
	electrochemistry		32
	hv		14
	hv		39
	M(III)Cl (M=Fe, Co, or Mn)		40

[a] These reactions had the immobilized molecule and soluble reagent reversed.

desorption/ionization and time-of-flight mass spectrometry (MALDI-TOF MS), when combined with monolayers in a technique termed SAMDI, provides rapid and definitive information on the products and yields of reactions on monolayers.[27,41] In this paper, we use the SAMDI method to report 15 reactions that occur on monolayers and we also demonstrate the use of SAMDI to rapidly screen a multitude of reaction conditions to identify an unanticipated interfacial reaction.

Experimental Section

Materials. Reagents and solvents were purchased from Aldrich Chemical Co. (Milwaukee, WI) unless otherwise noted. Tri-*tert*-butylphosphine (10 wt % in hexane) was purchased from Strem Chemicals, Inc. (Newburyport, MA), and absolute ethanol was purchased from AAPER Alcohol (Shelbyville, KY). Tetrahydrofuran (THF) was distilled from sodium/benzophenone, and dichloromethane was distilled from calcium hydride. Microscope cover glasses and glass vials (7 mL) with plugs and septa were purchased from Fischer Scientific (Pittsburgh, PA).

Preparation of Monolayers. Monolayers were prepared according to reported methods.[26] Briefly, 6 nm of titanium followed by 22 nm of gold were evaporated by electron beam onto glass microscope slides. Self-assembled monolayers were formed by immersion of the metallized slides in an ethanolic solution containing a functionalized alkanethiol (or disulfide) and a background alkanethiol (or disulfide) at an appropriate ratio (1 mM total thiol/disulfide concentration) at room temperature. After 12 h, the substrates were rinsed with ethanol and dried under a stream of nitrogen. Single reactions were performed with monolayers measuring approximately 4 mm^2 in glass vials. For the reaction screening, a larger substrate was placed in contact with a slab of poly(dimethylsiloxane) (PDMS) having an array of holes measuring 2 mm in diameter to give an array of reaction wells wherein the floors of the wells presented monolayers of defined composition.

SAMDI Mass Spectrometry Analysis. Monolayers were treated with 2,4,6-trihydroxyacetophenone (1 μL of a 5 mg/mL solution in acetonitrile or 10:1 v/v hexane/ethanol), allowed to dry in air, and analyzed on a Voyager DE-PRO Biospectrometry mass spectrometer from Applied Biosystems (Framingham, MA). A 337 nm nitrogen laser was used as the desorption/ionization source, and all spectra were acquired with 20 kV accelerating voltage using positive ion reflector mode.

Synthesis of Octadec-17-enyl-4-methylbenzenesulfonate (2). 11-Bromo-1-undecene (3.63 mL, 16.7 mmol) in THF (30 mL) was added dropwise to a reaction flask containing magnesium (0.6 g, 25 mmol) and a few crystals of iodine. The reaction mixture was heated at reflux for 2 h and then transferred dropwise to a solution of 1,7-*di*-tosyloxyheptane (**1**)[42] and copper(I) iodide in THF (30 mL). The reaction was kept at 50 °C for 14 h and then stopped by the addition of an aqueous solution saturated with ammonium chloride. The mixture was extracted with diethyl ether (30 mL × 3), and the combined organic layers were washed with water and brine and dried over anhydrous $MgSO_4$. After removal of the solvents *in vacuo*,

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the residue was purified by silica gel chromatography with 9:1 hexane/ethyl acetate as eluent to give **2** (3.01 g, 7.13 mmol, yield 42.7%). ^{1}H NMR ($CDCl_3$): 1.25 (m, 26H), 1.60 (m, 2H), 2.04 (m, 2H), 2.45 (s, 3H), 4.02 (t, 2H), 4.95 (m, 2H), 5.80 (m, 1H), 7.34 (d, 2H), 7.78 (d, 2H).

Synthesis of 2-(2-(2-(Octadec-17-enyloxy)ethoxy)ethoxy)ethanol (3). Sodium hydride (0.21 g, 8.7 mmol) was added to a solution of tri(ethylene glycol) (3.1 mL, 23.2 mmol) in anhydrous THF (30 mL). The solution was stirred for 2 h, and a solution of **2** in THF (30 mL) was added dropwise. The reaction was then heated at reflux for 16 h and then quenched with water. The mixture was extracted with ethyl acetate (30 mL × 3), and the combined organic layers were washed with water and brine and dried over anhydrous $MgSO_4$. After removal of the solvents *in vacuo*, the residue was purified by silica gel chromatography with 1:1 hexane/ethyl acetate as eluent to give **3** (1.78 g, 4.45 mmol, yield 76.6%). ^{1}H NMR ($CDCl_3$): 1.25 (m, 26H), 1.58 (m, 2H), 2.04 (m, 2H), 3.45 (t, 2H), 3.66 (m, 12H), 4.95 (m, 2H), 5.80 (m, 1H).

Synthesis of *S*-18-(2-(2-(2-Hydroxyethoxy)ethoxy)ethoxy)-octadecylethanethioate (4). Recrystallized azobis(isobutyronitrile) (AIBN) (50 mg) and thiolacetic acid (1.31 mL, 18.32 mmol) were added to a solution of **3** (1.83 g, 4.58 mmol) in MeOH (50 mL). The reaction mixture was stirred under a UV source for 12 h. The solvent was then removed under vacuum, and the product (**4**) was used without further purification. ^{1}H NMR ($CDCl_3$): 1.25−1.58 (m, 32H), 2.32 (s, 3H), 2.86 (t, 2H), 3.45 (t, 2H), 3.66 (m, 12H).

Synthesis of 2-(2-(2-(18-Mercaptooctadecyloxy)ethoxy)ethoxy)-ethanol (5). Concentrated HCl (5 mL) was added to a solution of thiolester **4** (2.17 g, 4.56 mmol) in MeOH (50 mL), and the reaction mixture was refluxed for 6 h. The solvent was then removed under vacuum, and the product (**5**) was used without further purification. ^{1}H NMR ($CDCl_3$): 1.25−1.58 (m, 32H), 2.52 (q, 2H), 3.45 (t, 2H), 3.66 (m, 12H).

Synthesis of 1,1,1-Triphenyl-21,24,27-trioxa-2-thianonacosan-29-ol (6). Trityl chloride (1.85 g, 6.63 mmol) was added to a solution of **5** (1.92 g, 4.42 mmol) in anhydrous THF (40 mL). The reaction mixture was stirred for 14 h. The solvent was then removed under vacuum, and the residue was purified by silica gel chromatography (1:2 hexane/ethyl acetate as eluent) to give **6** (1.35 g, 2.0 mmol, yield 45%). ^{1}H NMR ($CDCl_3$): 1.16−1.58 (m, 32H), 2.14 (t, 2H), 3.45 (t, 2H), 3.66 (m, 12H), 7.18−7.42 (m, 15H).

Synthesis of 1,1,1-Triphenyl-21,24,27,30-tetraoxa-2-thiatritriacont-32-yne (7). Sodium hydride (0.11 g, 4.5 mmol) was added to a solution of **6** (1.01 g, 1.5 mmol) in anhydrous dimethylformamide (DMF) (15 mL) at 0 °C. The reaction mixture was stirred at room temperature for 2 h and cooled to 0 °C, and then propargyl bromide (80 wt % in toluene, 0.5 mL, 4.5 mmol) was added dropwise. The solution was stirred at room temperature for 12 h and then quenched with water. The mixture was extracted with ethyl acetate (15 mL × 3), and the combined organic layers were washed with water and brine and dried over anhydrous $MgSO_4$. After removal of the solvents *in vacuo*, the residue was purified by silica gel chromatography (3:1 hexane/ethyl acetate as eluent) to give **7** (0.89 g, 1.25 mmol, yield 83%). ^{1}H NMR ($CDCl_3$): 1.16−1.58 (m, 32H), 2.12 (t, 2H), 2.42 (t, 1H), 3.45 (t, 2H), 3.66 (m, 12H), 4.21 (d, 2H), 7.18−7.42 (m, 15H).

Synthesis of 4,7,10,13-Tetraoxahentriacont-1-yne-31-thiol (8). Triethylsilane (0.16 mL, 1 mmol) and trifluoroacetic acid (0.4 mL) were added to a solution of **7** (0.14 g, 0.2 mmol) in anhydrous methylene chloride (3.6 mL). The reaction mixture was stirred for 2 h. The solvents were then removed under vacuum, and the residue was purified by silica gel chromatography (4:1 hexane/ethyl acetate as eluent) to give **8** (0.047 g, 0.1 mmol, yield 50%). ^{1}H NMR ($CDCl_3$): 1.25−1.58 (m, 32H), 2.42 (t, 1H), 2.52 (q, 2H), 3.45 (t, 2H), 3.57−3.72 (m, 12H), 4.21 (d, 2H).

Synthesis of 4,7,10,13-Tetraoxatetracos-1-yne-24-thiol (9). The synthesis of **9** was identical to that of **8** except that 11-bromo-1-undecene was used in place of **2**. ^{1}H NMR ($CDCl_3$): 1.25−1.58 (m, 18H), 2.42 (t, 1H), 2.52 (q, 2H), 3.45 (t, 2H), 3.57−3.72 (m, 12H), 4.21 (d, 2H).

Synthesis of 1,1,1-Triphenyl-14,17,20,23-tetraoxa-2-thiahexacosane-26-nitrile (16). Sodium hydroxide (3 mg) was added to a solution of **15** (0.17 g, 0.3 mmol) in acetonitrile (5 mL). The reaction flask was wrapped with aluminum foil, and acrylonitrile (0.03 mL, 0.45 mmol) was added dropwise. The reaction mixture was stirred for 3 h and then quenched with water. The mixture was extracted with dichloromethane (5 mL × 3), and the combined organic layers were washed with brine and dried over anhydrous $MgSO_4$. After removal of the solvents *in vacuo*, the product (**16**) was used without further purification. ^{1}H NMR ($CDCl_3$): 1.16−1.58 (m, 18H), 2.12 (t, 2H), 2.63 (t, 2H), 3.44 (t, 2H), 3.57−3.74 (m, 16H), 7.18−7.42 (m, 15H).

Synthesis of 1,1,1-Triphenyl-14,17,20,23-tetraoxa-2-thiahexacosan-26-amine (17). Lithium aluminum hydride (220 μL, 2.0 M in THF) was added to a solution of **16** (0.14 g, 0.22 mmol) in dry ethyl ether at −30 °C. The reaction mixture was stirred at −10 °C for 30 min and then quenched with an aqueous solution saturated with ammonium chloride. The mixture was extracted with dichloromethane (10 mL × 3), and the combined organic layers were washed with brine and dried over anhydrous $MgSO_4$. After removal of the solvents *in vacuo*, the residue was purified by silica gel chromatography (10:1 methylene chloride/methanol as eluent) to give **17** (12.7 mg, 0.02 mmol, yield 9.1%). ^{1}H NMR ($CDCl_3$): 1.16−1.58 (m, 20H), 2.08 (t, 2H), 2.13 (t, 2H), 3.13 (t, 2H), 3.52 (t, 2H), 3.57−3.74 (m, 14H), 7.18−7.42 (m, 15H).

Synthesis of 1-Amino-4,7,10,13-tetraoxatetracosane-24-thiol (18). Triethylsilane (0.016 mL, 0.1 mmol) and trifluoroacetic acid (0.15 mL) were added to a solution of **17** (12.7 mg, 0.02 mmol) in anhydrous methylene chloride (2.85 mL) and stirred for 2 h. The solvents were then removed, and the residue was purified by silica gel chromatography (10:1 methylene chloride/methanol as eluent) to give **18** (3.8 mg, 0.01 mmol, yield 48.3%). ^{1}H NMR ($CDCl_3$): 1.25−1.58 (m, 20H), 2.08 (t, 2H), 2.52 (q, 2H), 3.13 (t, 2H), 3.52 (t, 2H), 3.57−3.74 (m, 14H).

***N*-Alkyl Pyridinium Formation (Table 2, Entry 16).** Propanal (7.3 μL, 0.1 mmol) and dimethyl sulfoxide (DMSO) (1 mL) were added to a glass vial. An amino-terminated monolayer (prepared from a 1:1 ethanolic solution of amino-terminated disulfide **14** and tri(ethylene glycol) disulfide **12**) was placed in the solution and kept at room temperature for 1 h. The monolayer was then removed, washed, and analyzed by SAMDI. Representative SAMDI spectra are shown in Figure 7.

Synthesis of 2-Ethyl-3,5-dimethyl-1-phenethylpyridinium (19). 2-Phenethylamine (0.28 mL, 1.5 mmol) and propanal (10.8 mL, 150 mmol) were dissolved in hexane (16 mL) and stirred at room temperature for 24 h. The solvent and excess propanal were then removed under vacuum, and the residue was purified by silica gel chromatography (10:1 methylene chloride/methanol as eluent) to give **19** (7.7 mg, 0.032 mmol, yield 2.1%). ^{1}H NMR (CD_3CN): 1.22 (t, 3H), 2.29 (s, 3H), 2.46 (s, 3H), 2.96 (q, 2H), 3.21 (t, 2H), 4.64 (t, 2H), 7.13 (m, 2H), 7.31 (m, 3H), 8.02 (s, 1H), 8.03 (s, 1H). MS (APCI$^+$): 240.1 (M^+). HRMS calcd for $C_{17}H_{22}N$ 240.1747, found 240.1745.

Results and Discussion

Overview. Table 2 summarizes 15 known reactions that we performed on self-assembled monolayers (SAMs) and one reaction that we discovered through a screening process. The 15 reactions were performed on monolayers presenting a terminal acetylene group (entries 1−5), a bromobenzene group (entry 7), a primary alcohol (entries 8−10 and 12), or a primary amine (entries 14−16), as well as functional groups that were generated through reactions of these groups (entries 6, 11, and 13). Below, we describe the synthesis of alkanethiol reagents, the preparation of the monolayers, the interfacial reactions, and an example of screening to identify unanticipated interfacial reactions. The Supporting Information provides the conditions employed for each reaction and the corresponding SAMDI spectra.

Synthesis of Alkanethiols. We synthesized several alkanethiol and disulfide reagents that were used to prepare the monolayers.

Table 2. Chemical Reactions on SAMs Performed in This Paper

Entry	SAM	Reactant	Condition	Product
1			NaH, D_2O	D
2		I	$Pd(PPh_3)_4$, CuI, TBAF, THF	
3		N–Br	$AgNO_3$, Acetone	Br
4		H_2O	$Au(PPh_3)Cl$, $AgOTf$, Toluene	O
5		Br—≡—TIPS	CuI, HO-NH_2·HCl, n-$BuNH_2$, H_2O, THF	TIPS
6	TIPS		TBAF, THF, 0 °C	
7	Br	HO, B, HO	$Pd_2(dba)_3$, $P(t\text{-}Bu)_3$, KF, THF	
8	OH	MeI	NaH, THF	OMe
9	OH	O	$BF_3{\cdot}Et_2O$, Et_2O	O, O, H, n
10	OH	O, O, P, O, N, N, N	PPh_3, DEAD, THF	N_3
11	N_3	PPh_3	THF	N, PPh_3
12	OH	TsCl	NaH, THF	OTs
13	OTs	EtO^- Na^+	EtOD	OEt
14	NH_2	O, O	MeOH	H, N, O, O
15	NH_2	O, O, O	DMF	H, N, O, OH
16	NH_2	O	DMSO	N+

We prepared the alkyne-terminated alkanethiol using a synthetic strategy that is commonly employed for substituted alkanethiols (Figure 1). Briefly, coupling 1,7-*di*-tosyloxyheptane **1** with one equivalent of (10-undecen-1-yl)magnesium bromide provided tosylate **2**, which was displaced with tri(ethylene glycol) to give the terminal alkene **3**. The olefin was converted to the thioester **4** by radical-mediated addition of thiolacetic acid and then hydrolyzed under acidic conditions to give the primary thiol **5,** which was subsequently protected as the trityl thioether **6**. The hydroxyl group of **6** was alkylated with propargyl bromide followed by removal of the trityl group (TFA) to give the alkyne-terminated alkanethiol **8**. In certain experiments, a related alkyne-terminated alkanethiol (**9**) having a shorter alkyl segment was used and was synthesized by the same route. In practice, the larger molecular weights of the longer alkanethiols provide for a clearer separation of the peaks for the alkanethiolates from those corresponding to the matrix in the SAMDI spectrum. The oxygen atoms may serve to increase the ionization efficiency of the alkanethiolates, but we have not fully characterized this possibility. The synthesis of the amino-terminated alkanethiol

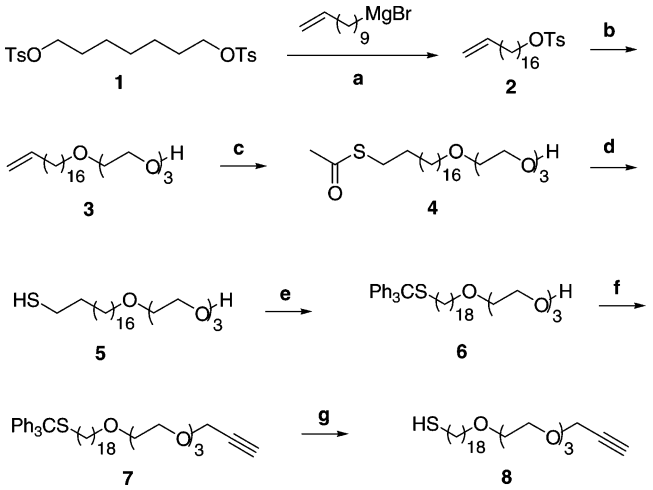

Figure 1. Synthesis of alkanethiol **8**: (a) CuI, THF; (b) tri(ethylene glycol), NaH, THF; (c) CH_3COSH, AIBN, MeOH, *hv*; (d) HCl, MeOH; (e) Ph_3CCl, THF; (f) propargyl bromide, NaH, DMF; and (g) TFA, TESH, CH_2Cl_2.

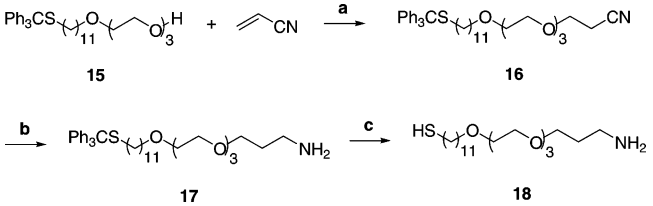

Figure 2. Synthesis of alkanethiol **18**: (a) NaOH, CH_3CN; (b) LAH, Et_2O; and (c) TFA, TESH, CH_2Cl_2.

followed a similar route (Figure 2). We started with a glycol-terminated protected alkanethiol (**15**)[39] and functionalized the hydroxyl group through addition to acrylonitrile. The cyano group was reduced with lithium aluminum hydride, and the trityl group was removed in trifluoroacetic acid to give the amino-terminated alkanethiol **18**. The tri(ethylene glycol)-terminated alkanethiol **11** and the corresponding disulfide **12** were synthesized as described previously.[26,43] A disulfide bearing one terminal amino group and one tri(ethylene glycol) group **14** was synthesized as described previously,[34] as was a disulfide presenting one maleimide group and one tri(ethylene glycol) group **13**.[26] The structures and molecular weights of the alkanethiols/disulfides are shown in Scheme 1.

Preparation of Monolayers. Monolayers presenting the terminal alkyne group were prepared by immersing a gold-coated slide into a solution of an alkyne-terminated alkanethiol (**8** or **9**) and 1-octadecanethiol or 1-undecanethiol in a ratio ranging from 7:3 to 1:9. Monolayers presenting a primary hydroxyl group were prepared from a solution of tri(ethylene glycol)-terminated alkanethiol **11** and 1-undecanethiol in a ratio of 1:1 or 1:9. Monolayers presenting the maleimide group were prepared from a solution of the maleimide-terminated disulfide **13** and a tri-(ethylene glycol)-terminated disulfide **12** in a ratio of 1:1. The amino-terminated monolayers were prepared from solutions of the amino-terminated alkanethiol **18** and 1-undecanethiol in a ratio of 7:3 or the amino-terminated disulfide **14** and tri(ethylene glycol)-terminated disulfide **12** in a ratio of 1:1. In each case, the monolayers were allowed to assemble from solutions for 12 h and were then rinsed with ethanol and dried under a stream of nitrogen.

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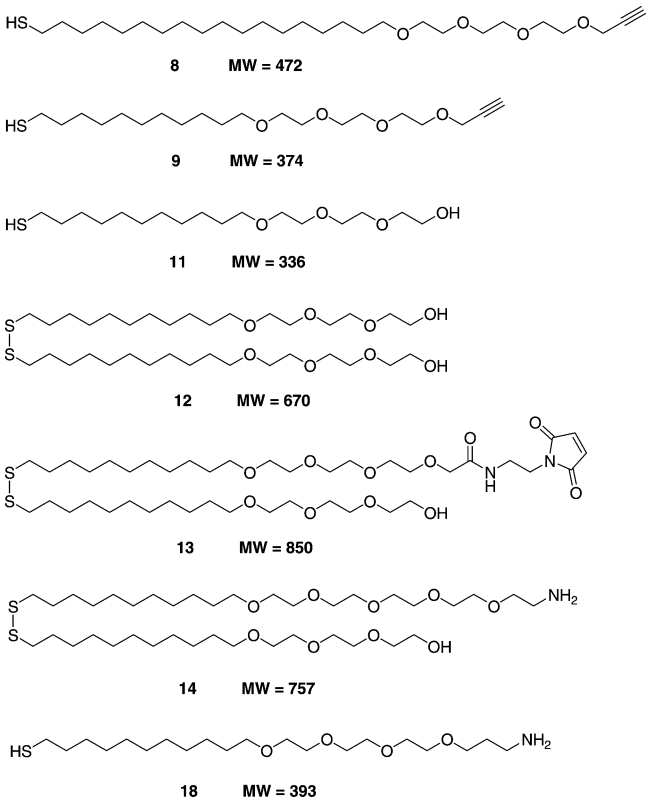
Scheme 1. Structures and Molecular Weights of Alkanethiol and Disulfide Reagents Used to Prepare Monolayers



Hydrogen−Deuterium Exchange. The first interfacial reaction started with a monolayer presenting the alkyne-group at a density of approximately 50%. A mass spectrum of this monolayer revealed peaks at mass-to-charge (*m*/*z*) ratios of 779 and 965 (Figure 3B), corresponding to the sodium adducts of the disulfides derived from one background and one alkyne-terminated alkanethiolate and from two alkyne-terminated alkanethiolates, respectively. As reported in our previous work, we find that disulfides are the predominant species observed in SAMDI analysis. The monolayer was immersed in a solution of NaOD in D_2O for 30 min, after which it was removed, rinsed with acetone, distilled water, and ethanol, dried, and analyzed by SAMDI. The resulting mass spectrum revealed a complete conversion of the initial peaks at *m*/*z* 779 and 965 to two new peaks at *m*/*z* 780 and 967 (Figure 3C) consistent with an exchange of the terminal proton with deuteron. This example is notable because the product would be difficult to identify conclusively with the traditional techniques used in characterizing monolayers. The starting material and product differ by a single neutron, yet SAMDI provides a clear resolution between the starting material peaks at *m*/*z* 779 and 965 and the product peaks at *m*/*z* 780 and 967.

Coupling Reactions. Reactions that serve to couple a soluble molecule with the monolayer are important for elaborating surfaces with biological or electronic functionality.[3,26,44,45] We performed several reactions to this end, including the Sonogashira coupling,[46] the Cadiot−Chodkiewicz coupling,[47] the Suzuki coupling,[48] and the Staudinger reaction[49] (entries 2, 5, 7, and 11 in Table 2). For the Sonogashira reaction, a monolayer presenting an alkyne group was treated with a solution of $Pd(PPh_3)_4$, CuI, PhI, and TBAF in THF for 30 min (Figure 4). The peaks at *m*/*z* 583 and 769 for the initial monolayer (corresponding to the sodium adducts of the disulfides derived from one background and one alkyne-terminated alkanethiolate and from two alkyne-terminated alkanethiolates, respectively) gave rise to the expected peaks at *m*/*z* 659 and 921 for the product (Figure 4C). The other reactions likewise proceeded efficiently to give the 1,3-diyne, biphenyl, and iminophosphorane adducts (see Supporting Information). The compatibility of SAMDI with the reagents employed in these reactions together with the straightforward implementation of this method make it convenient for rapidly optimizing the reaction conditions to give high yields of the interfacial

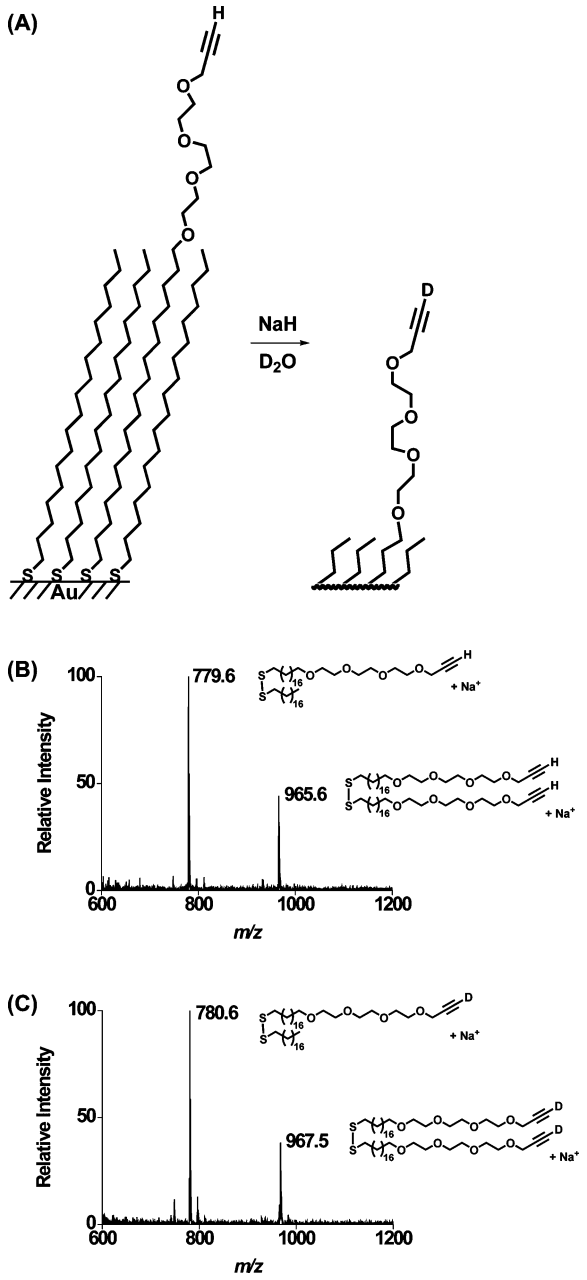


Figure 3. (A) A monolayer presenting a terminal acetylene group was treated with D_2O and base to promote the deuteration reaction. SAMDI mass spectra before (B) and after (C) the reaction show the high yield conversion and good mass resolution of SAMDI.

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(46) Mori, A.; Shimada, T.; Kondo, T.; Sekiguchi, A. *Synlett* **2001**, 649−651.
(47) Marino, J. P.; Nguyen, H. N. *J. Org. Chem.* **2002**, *67*, 6841−6844.
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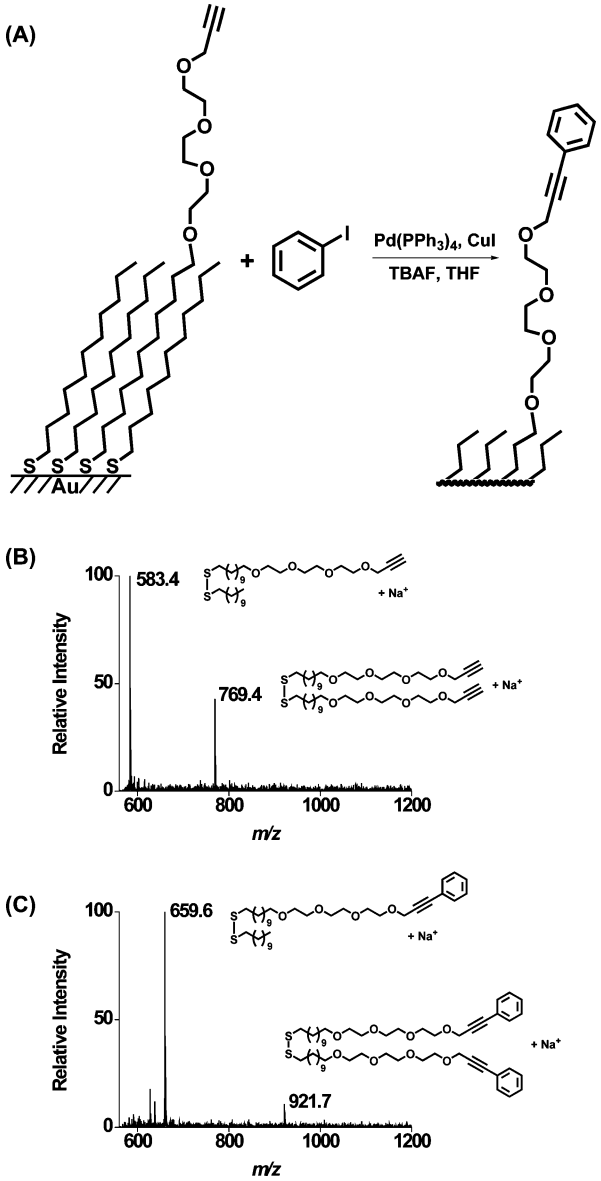

Figure 4. (A) A monolayer presenting a terminal acetylene group was treated with $Pd(PPh_3)_4$, CuI, PhI, and TBAF to give the phenylacetylene. SAMDI spectra before (B) and after (C) the reaction show that the reaction proceeded in high yield.

conversions. From this work, we suggest that the high efficiency of the Sonogashira reaction and the wide variety of commercially available aromatic iodide compounds make this conversion particularly attractive for use in modifying surfaces.

Multistep Reaction Sequences. We also show that SAMDI is well suited for characterizing the efficiencies of multistep reaction sequences on the monolayer (Table 2, entries 5, 6, and 10−13). In one example, we started with a monolayer presenting a primary hydroxyl group and carried out a Mitsunobu reaction to generate the corresponding monolayer that presents an azide group (entry 10 in Table 2). SAMDI analysis of the initial monolayer revealed peaks at *m*/*z* 545 and 693 (Figure 5B) corresponding to the sodium adducts of the disulfides derived from one background and one hydroxyl-terminated alkanethiolate and from two hydroxyl-terminated alkanethiolates, respectively. After treatment of the monolayer with a solution containing diphenylphosphoryl azide (DPPA), PPh_3, and diethyl azodicarboxylate (DEAD) in THF for 1 h (Figure 5), the SAMDI spectra revealed the expected peak at *m*/*z* 570 (Figure 5C) corresponding to the sodium adduct of the disulfide derived from one background and one azide-terminated alkanethiolate, with a second peak at *m*/*z* 703 corresponding to a side product resulting from nucleophilic substitution of the phosphonium intermediate by DEAD. We then carried out a Staudinger reaction by treating an identical monolayer with a solution of PPh_3 in THF for 1 h. Analysis of the resulting monolayer by SAMDI revealed that the original peak at *m*/*z* 570 was efficiently converted to a peak at *m*/*z* 596 and 782. The first peak represents the proton adduct of the monosulfide of the iminophosphorane product, and the latter represents the proton adduct of the mixed disulfide. In this example, the predominant peaks were derived from protonated adducts of the alkanethiolates, with minor peaks that correspond to the sodium adducts at *m*/*z* 618 and 804. We also observed peaks at *m*/*z* 562 and 750, which correspond to loss of the sulfur from the alkanethiolates and which we occasionally observe as minor species in the SAMDI spectra.

We performed several additional reactions that serve to demonstrate the range of reagents that are compatible with monolayers and to provide chemical routes to elaborating the structures of monolayer substrates. We demonstrated, for example, the bromination of a terminal acetylene (entry 3) and hydration to afford the corresponding methyl ketone (entry 4). Similarly, we report reactions of hydroxyl-substituted monolayers, including alkylation with alkylhalides to form ethers (entry 8) and with epoxides to form glycols (entry 9). Finally, we report the reaction of primary amines with carbonyl reagents to provide acetoacetamide and maleamic acid products (entries 14 and 15, respectively). The conditions and SAMDI spectra for each of these conversions are provided in the Supporting Information.

Estimation of Yields. A significant benefit of SAMDI relative to other analytical techniques is that it simultaneously provides data on the presence of both the reactant and the product and therefore provides an estimate of the yields of interfacial reactions. In the hydration of a terminal acetylene to provide the methyl ketone (entry 4 in Table 2), for example, SAMDI shows a peak for the appearance of the product (at 797 Da) as well as a peak corresponding to the reactant. Absent the SAMDI method, IR spectroscopy would have been the preferred method for analyzing this reaction because it can measure the characteristic stretching frequency of the carbonyl group. Yet, the weak intensities for vibrations of the carbon−carbon triple bond make it difficult to quantitate the amount of reactant and therefore difficult to determine the yield of the reaction. We note that SAMDI also has limitations in providing quantitative measures of reaction yields. Because the intensity of the peak observed in the spectrum is dependent on the mass and the properties of the parent ion, the intensities of peaks corresponding to different structures cannot be directly compared to give quantitative information on the relative density of each species. For experiments that require quantitative results, it is necessary to first calibrate the intensities of each peak. The calibration can be performed by preparing monolayers having only the component of interest at a defined density and normalizing the peak intensity for the substituted alkanethiolates relative to the peak intensity for the background alkanethiolate (that is, the alkanethiolate that does not participate in the reaction). For rapid screening of reactions (as described below), this calibration is not practical, and therefore, we recognize that SAMDI does not provide rigorous quantitative information on the extent of reaction.

Incompatibility of Monolayers with Reagents. While we were successful in performing several new reactions of SAMs, we also found that several established reactions failed to give the expected product when performed on the monolayer. For example, we found that the attempted reduction of an azide-

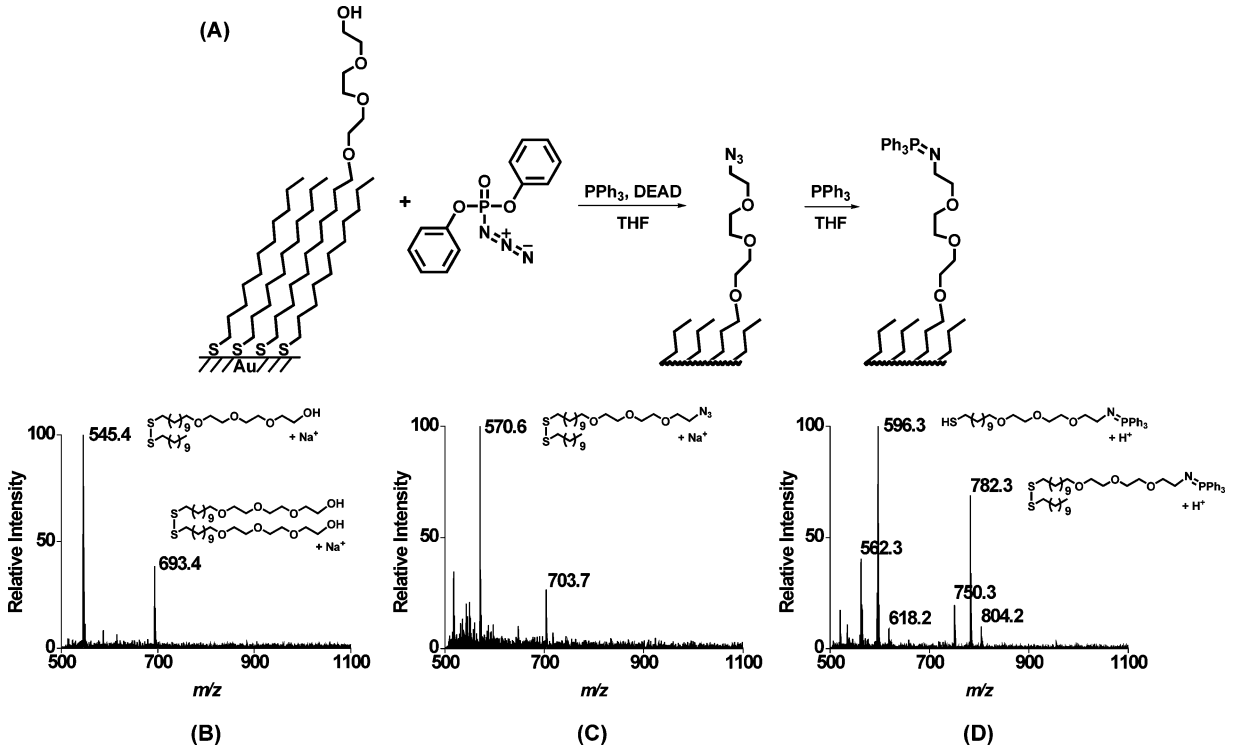

Figure 5. (A) A monolayer presenting a terminal alcohol group was treated with DPPA, PPh_3, and DEAD to convert the alcohol group to the azide group. The azide-terminated SAM was then treated with PPh_3 to give the iminophosphorane product. SAMDI spectra before (B) and after (C and D) each reaction show that the reactions proceeded in high yields.

terminated SAM with $LiAlH_4$ to provide the corresponding primary amine did not proceed, although the monolayer was stable to the reagent. This lack of reactivity may be a consequence of the environment at the solid−liquid interface, which can differ substantially from that in homogeneous solution. Steric effects, chemical interactions with functional groups of the monolayer, and geometric constraints may play a role in determining whether the energy barrier for an interfacial reaction is surmountable.[5] We found other cases where the monolayers were not stable to reagents. It is well-known, for example, that the thiolate group that anchors the monolayer to the gold film undergoes spontaneous oxidation if exposed to the atmosphere for prolonged periods[50] and that monolayers can be thermally desorbed at temperatures greater than 70 °C.[51] In our screening of reactions, we found that monolayers were not stable in the presence of strong oxidants (for example, ozone,[50] $KMnO_4$, and iodine), several Lewis acids (for example, Au^{3+}, Hg^{2+}, and Ru^{3+}), highly basic conditions (for example, high concentration of sodium hydroxide), and, on certain occasions, combinations of reagents (for example, the monolayer was stable to a THF solution of either carbon tetrabromide (1 mM) or triphenylphosphine (1 mM) but not to a solution containing both reagents). In each of these cases, the monolayer was completely degraded and we did not observe peaks corresponding to any alkanethiol species. We also observed partial damage of the monolayers under certain conditions. For example, in Table 2 entry 13, although treatment with ethoxide gave the desired product, the quality of the mass spectrum, as shown by the signal-to-noise in Figure S7 of the Supporting Information, is degraded, which may suggest a loss of alkanethiolates from the gold substrate.

Notwithstanding these findings of reagents that are not compatible with monolayers, we did find that a broad range of reactions could be performed on SAMs. We have found that the time of reaction was often important, with most reactions proceeding efficiently within 1 h, but with deterioration of the monolayer with significantly longer times (as evidenced by SAMDI spectra with lower signal-to-noise). The method used to stop the reaction and rinse the monolayer was also often significant in obtaining good SAMDI spectra. Specifically, the use of acetone, water, and ethanol to rinse the monolayers was usually sufficient, but a subsequent treatment of the monolayer with solvents that dissolve adsorbed species was necessary. For example, for entry 3 in Table 2, the surface was cleaned with dilute ammonium hydroxide to remove silver bromide precipitate. Finally, we note that the current work did not exhaustively evaluate possible reaction conditions that may be used to elaborate the structures of monolayers. Using the method described here, it is straightforward to evaluate any number of reactions of self-assembled monolayers.

Reaction Screening. The results reported above establish that SAMDI is well-suited to the rapid evaluation of products and yields of chemical reactions performed on SAMs. The ability to obtain this information from a small region of the substrate (approximately 1 mm^2) together with the generality in characterizing a broad range of reactions (because the use of mass spectrometry avoids the need for labeling strategies) suggests that this strategy may be valuable for the *de novo* screening of novel reactions. Current approaches to reaction screening have aimed to identify optimal reagents and conditions for a specific conversion. For example, Miller and co-workers demonstrated a screen to identify, from a peptide library, catalysts for enatioselective transacetylation reactions.[52] This example utilized a protonation-dependent fluorophore to report on the reaction, whereas other approaches utilize IR or spectrophotometry to detect a spectroscopic transition that is specific to the product.[53]

(50) Schoenfisch, M. H.; Pemberton, J. E. *J. Am. Chem. Soc.* **1998**, *120*, 4502−4513.

(51) Bain, C. D.; Troughton, E. B.; Tao, Y. T.; Evall, J.; Whitesides, G. M.; Nuzzo, R. G. *J. Am. Chem. Soc.* **1989**, *111*, 321−335.

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It is this need for a labeling strategy that limits a broader implementation of chemical screening methods. This limitation is particularly significant in the search for *unanticipated* reactions, where prior knowledge of the reaction, and therefore the functional groups present in the product, is not available.

Liu and co-workers have described a strategy that can screen many reaction conditions to identify those that give a covalent adduct between two functional groups.[54] In this method, a DNA template is used to organize two oligonucleotides such that their termini, which are modified with common organic functional groups, are brought in proximity. In the presence of the appropriate reagents, certain groups will react to form an adduct. The resulting tethered oligonucleotides are selected, and their sequences are determined by hybridization to a DNA microarray, revealing the identities of the functional groups that reacted. This approach has the benefit that it does not require prior knowledge of the reaction type to be discovered and that it can be performed in a highly multiplexed fashion. The limitations are that only reactions that result in the formation of an adduct between the two reactants (and not those that involve transfer of an atom or fragment from one reagent to the other) can be detected, the screening method does not provide information on the nature of the product, and the use of DNA strands limits the choice of solvents and reagents that are employed in the screen.

The SAMDI method complements these existing strategies for reaction screening in that it can identify all products that have a mass distinct from the reactant (which omits isomerization and internal rearrangement reactions) without the use of labels. We performed a limited screening program to validate this approach. We prepared separate monolayers that were substituted with alkyne, amine, or alcohol groups and diluted with 1-undecanethiol as background. We generated microwells having the monolayer as the bottom surface by placing a slab of poly(dimethylsiloxane) (PDMS) with an array of holes directly in contact with the monolayer. We then applied solutions of various reagents in DMSO (40 mM, 30 μL, Figure 6) in each well and allowed reactions to proceed at room temperature for 1 h. We then aspirated the solutions from each well, removed the PDMS film, and rinsed the monolayer with acetone, water, and ethanol. We applied matrix and analyzed each circular region by mass spectrometry. We inspected each spectra and discarded those that showed no reaction (that is, the only peaks in the spectra corresponded to the reactants in the monolayer) and those that gave multiple peaks with no single pronounced reaction product. For the spectra that gave a clean conversion of the reactant to a product (where we used as a cutoff an approximate yield of 50%), we could identify several that corresponded to known reactions and these were not considered further.

In one example, we treated an amino-terminated SAM (prepared from an ethanolic solution of the amino-terminated alkanethiol **18** and 1-undecanethiol in a ratio of 7:3) with the array of reagents shown in Figure 6. The majority of the SAMDI spectra had a single pronounced peak at *m*/*z* 602, corresponding to the sodium adduct of the disulfide derived from one background and one amino-terminated alkanethiolate, and therefore, they represent combinations that did not promote reactions. For several combinations, we observed peaks that were consistent with expected reactions. For example, the *m*/*z* 602 peak that was originally present in region 4A of the array gave rise to a new peak at *m*/*z* 644 as is expected for the amide that results from acylation of the amine. Similarly, for region 4D, we observed a peak at *m*/*z* 735 that corresponds to the imine formed between

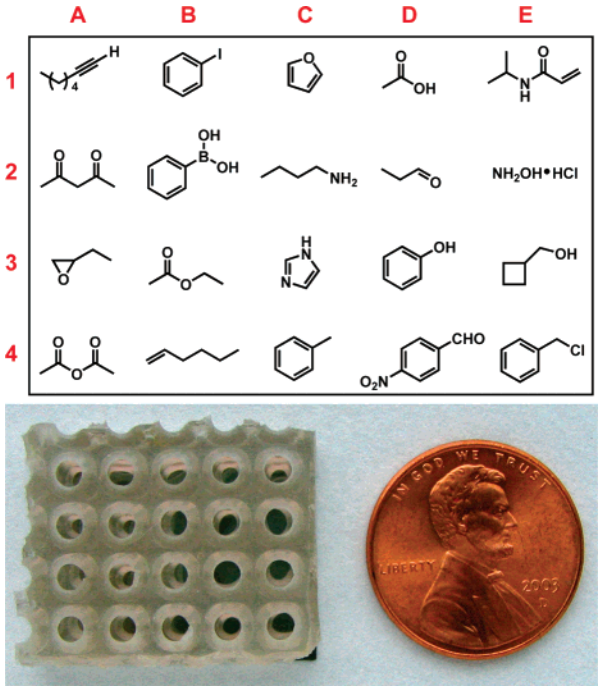

Figure 6. A monolayer presenting primary amino groups was treated with an array of reagents (shown in the top panel). Reaction wells were created by applying a polymeric slab having an array of holes to the monolayer (bottom panel).

4-nitrobenzaldehyde and the amine. We observed one spot (region 2D in the figure) that gave a strong peak representing a product that we could not immediately identify, and we address this result next.

Treatment of a monolayer presenting a primary amine group with propanal (100 mM in DMSO) at room temperature for 1 h resulted in a near-complete conversion of the amino-terminated alkanethiol to an unknown product of higher mass (Figure 7). For the following experiments, we used (1-mercaptoundec-11-yl)-tri(ethylene glycol) instead of 1-undecanethiol as the background alkanethiolate in the monolayer because the disulfide formed between this molecule and the product alkanethiolate provides a higher intensity signal in the SAMDI spectrum. The amino-terminated disulfide in the parent monolayer gave a peak at *m*/*z* 780, corresponding to the sodium adduct of this species. After reaction, this peak was absent and gave rise to a peak at *m*/*z* of 876. Assuming this peak corresponds again to the heterodisulfide species as the sodium adduct, the product has a mass that is 96 Da greater than the reactant amine. This difference in mass clearly requires that more than one aldehyde molecule reacted with the amine and for this reason rules out the formation of the expected imine product.

To probe the structure of an unknown product, experiments can be repeated with isotopically labeled reactants (or reactants having additional molecular fragments) to understand the relationship between the structures of the reactants and products. In this way, we performed several experiments that confirmed that the adduct resulted from reaction of the amine with three aldehyde molecules. First, when we repeated the experiment with butanal (which has one additional methylene group), the product had a mass that was greater than that observed with propanal by 42 Da, implying the incorporation of three aldehydes. The same experiment with valeraldehyde gave the analogous result. Further, when a reaction was performed with a mixture of propanal and butanal, we observed four products that were each spaced by a mass of 14 Da (Figure 8), again consistent with the incorporation of three aldehyde units in the product. Finally,

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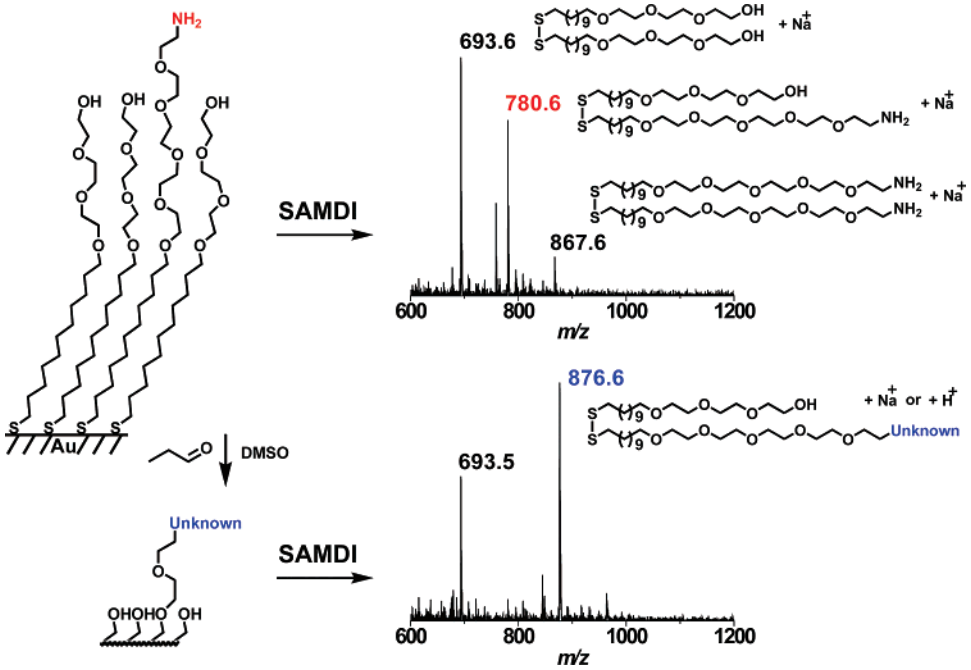
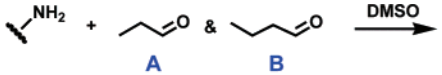


Figure 7. A monolayer presenting a primary amine group treated with propanal solution gave an unexpected reaction product. SAMDI spectra before and after the reaction show that the reaction proceeded in high yield.



Aldehyde per Product	Possible Products	# of Peaks
1	A, B	2
2	AA, AB, BB	3
3	AAA, AAB, ABB, BBB	4

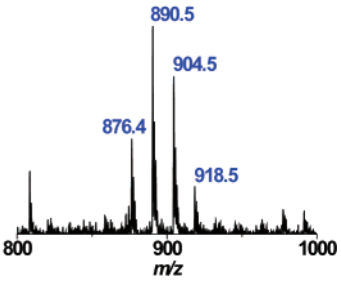
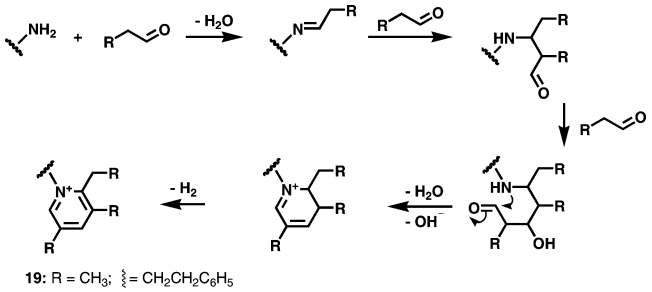


Figure 8. A monolayer presenting a primary amine group was treated with the mixture of propanal and butanal solution to verify the number of aldehydes incorporated in the product. SAMDI spectra after the reaction prove that three aldehyde units were incorporated in the product.

Scheme 2. Proposed Mechanism for an Amino-Terminated Monolayer Reacting with Aldehydes



19: R = CH_3; ⦚ = $CH_2CH_2C_6H_5$

the use of an isotopically labeled aldehyde, *n*-nonaldehyde-1-^{13}C, gave a product had a mass that was 3 Da greater than that for the nonlabeled aldehyde, which also establishes that each of the three carbonyl carbon atoms is present in the product.

These data led us to postulate the formation of an *N*-alkyl pyridinium product (Scheme 2) resulting from condensation of three aldehydes with the amine on the surface, followed by ring closure and oxidation. To verify our hypothesis, we performed the reaction in solution with 2-phenethylamine and propanal with the latter in large excess. We used 100 equiv of aldehyde to approach the stoichiometry that is used in the interfacial reaction conditions. We isolated a product (**19**) in 2% yield that corresponded to the pyrdinium adduct shown in Scheme 2. This reaction is reminiscent of the Chichibabin reaction,[55,56] except that on the monolayer it proceeds under mild conditions and does not require elevated temperature or high pressure. A report by Wang and co-workers also demonstrated a mild condensation of aldehydes and alkylammonium chlorides to give 2,3-dihydropyridinium and pyridinium derivatives. That reaction was catalyzed by lanthanide triflate salts and proceeded over a period of 24 h in aqueous solution.[57] It is notable that the interfacial reaction we report here is complete in 1 h and does not require a catalyst. This efficient reaction may owe to the large excess of the aldehyde in solution, the immobilization of the amine (which prevents diffusion of the amine and reaction with other amine-derived intermediates), and the interfacial environment that may provide stabilization of the transition state(s) in the rate-determining step(s). In any event, this example reveals the efficiency with which an unanticipated interfacial reaction can be discovered using the SAMDI method, and it adds an example that highlights the different reactivities that can accompany common functional groups when immobilized to a solid surface. We believe that the screening procedure reported here can be expanded to a much broader set of reagents and reactants to discover other reactions.

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Conclusions

This manuscript demonstrates that SAMDI-TOF mass spectrometry is well-suited for characterizing the products and yields of reactions that occur on self-assembled monolayers of alkanethiolates on gold, and in turn it represents an important addition to the current analytical methods now employed to characterize the structures of monolayers. This method enabled the rapid screening of a broad range of known reactions on monolayers and the optimization of conditions to give high yielding conversions. Absent SAMDI, the characterization of several of the reactions would have been very difficult. We are most encouraged by the suitability of this method for screening reaction products. The absence of labeling strategies when working with SAMDI makes it straightforward to tailor the structures of monolayers for diverse applications and provides an efficient method to identify reactions that give unanticipated products.

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Supporting Information Available: Experimental procedures for each reaction reported in Table 2 and SAMDI mass spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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