Self-assembled multilayers of ω-mercaptoalkanoic acids: Selective ionic interactions

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Scheme I[a]

7; $R^1 = H, R^2 = R^3 = \beta DGlcNAc;$

8; $R^1 = H, R^2 = R^3 = PhCO$

9; $R^1 = \beta DGlcNAc, R^2 = R^3 = H$

10; $R^1 = H, R^2 = R^3 = \beta DGal(1-4)\,\beta DGlcNAc$

11; $R^1 = \beta DGal(1-4)\,\beta DGlcNAc, R^2 = R^3 = H$

1; $R^1 = H, R^2 = \alpha DNeuAc(2-6)\beta DGal(1-4)\,\beta DGlcNAc,$
$R^3 = \beta DGal(1-4)\,\beta DGlcNAc$

2; $R^1 = H, R^2 = R^3 = \alpha DNeuAc(2-6)\beta DGal(1-4)\,\beta DGlcNAc$

3; $R^1 = \alpha DNeuAc(2-6)\beta DGal(1-4)\,\beta DGlcNAc, R^2 = R^3 = H$
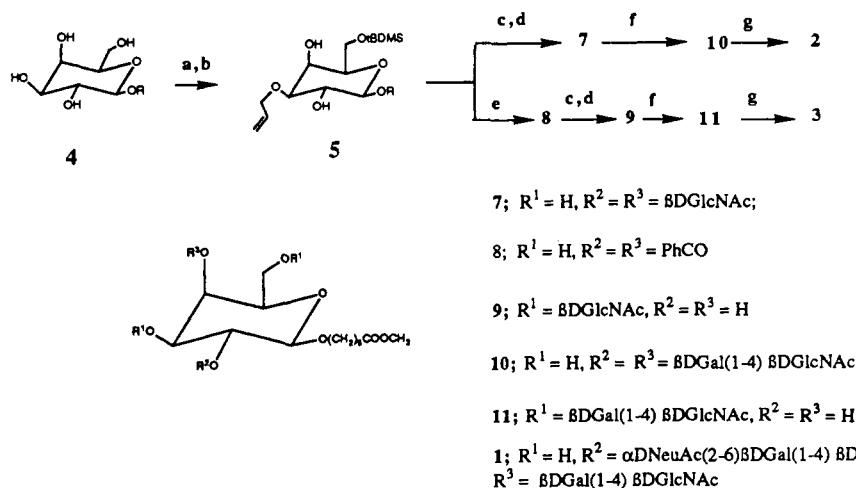
[a] (a) n-Bu₂SnO–benzene, Et₄NBr, allyl bromide; (b) TBDMSCl–DMF; (c) 2-deoxy-3,4,6-tri-O-acetyl-2-phthalimido-α,β-D-glucopyranosyl bromide–AgOTf–collidine–CH₃NO₂; (d) NaOMe–MeOH; H₂NNH₂–MeOH; Ac₂O–pyridine; NaOMe–MeOH; (e) PhCOCl–pyridine; Ir(COD)-[Ph₂Me]₂PF₆–THF; 10% HgCl₂–90% aqueous acetone; (f) UDP-galactose–bovine galactosyltransferase; (g) CMP-NeuAc–2,6 sialyltransferase.

to the digalactosylated pentasaccharides **10** and **11** in one step using UDP-galactose and bovine galactosyltransferase (EC 2.4.1.22) followed by purification on a column of Bio Gel P2. Monogalactosylated intermediates were not seen in these reactions. The pentasaccharides were converted to the heptasaccharides **2** and **3** by using CMP-NeuAc and Galβ1,4GlcNAcβ 2,6 sialyltransferase[16] (EC 2.4.99.1). The disialosides were obtained as the major products along with minor monosialosides (**1**[17] was obtained as a byproduct in the enzyme reaction with **10**; even though **1** could be converted to **3**, we used it as a control in the binding assays). They were easily separated by adsorption on an ion-exchange column followed by successive elution with 5 and 50 mM phosphate buffer. The structural identities of **2** and **3** were confirmed by ¹H and ¹³C NMR (¹H NMR spectra of the tri-, penta-, and heptasaccharides are provided in the supplementary material).

The inhibitory potencies of the synthetic disialosides were evaluated by titration of the synthetic compounds in a quantitative biological assay involving virus adsorption to resialylated erythrocytes as described by Pritchett et al.[3b] These kinetic inhibition assays are sensitive enough to reliably detect compounds that differ in inhibitory potencies by as little as 2-fold. As shown in Table I, the inclusion of neutral sugars as seen in the monovalent sialoside **1** makes it a 2-fold-better inhibitor than methyl α-D-sialoside. When the second sialic acid was added on the other lactosamine arm of **1** to give **2**, the inhibition efficiency increased only marginally to 1.5-fold, but weaker than the monosialoside **1**. However, when two sialic acids were placed in such a way as to keep them farthest apart as seen in compound **3**, then the inhibitory potency increased by as much as 10-fold.

This represents the first demonstration[18] of increased inhibitory potency by a synthetic, low molecular weight, bivalent sialoside and exemplifies the importance of cluster oligosaccharide effects for binding toward proteins.

Preparation of other heptasaccharides where the distance between the two sialic acids has been systematically varied, as well as the immobilization of the disialosides (via the linker arm attached to the anchoring galactose) on protein matrix such as bovine serum albumin, is in progress. We are also investigating the conformational properties of these molecules by 600-MHz NMR spectroscopy to understand the structure–inhibitory activity relationship.

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(16) Weinstein, J.; de Souza-e-Silva, U.; Paulson, J. C. *J. Biol. Chem.* **1982**, *257*, 13835–13844.

(17) The structure of the monosialosides **1** is tentatively assigned as

αDNeuAc(2–6)βDGal(1–4)βDGlcNAc(1–2)
                  βDGal–O(CH₂)₅COOCH₃
βDGal(1–4)βDGlcNAc(1–4)
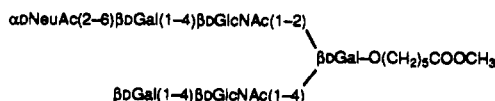
(18) A related publication has recently appeared. Glick, G. D.; Knowles, J. R. *J. Am. Chem. Soc.* **1991**, *113*, 4701–4703.

Self-Assembled Multilayers of ω-Mercaptoalkanoic Acids: Selective Ionic Interactions

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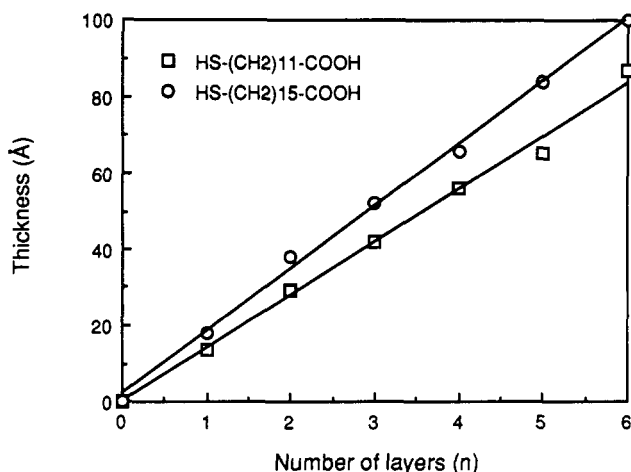
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Self-assembled (SA) monolayers are molecular assemblies that are *spontaneously* formed by the immersion of an appropriate substrate into a solution of an active surfactant.[1] This technique provides a potentially attractive route for the formation of systems ordered at the molecular level. That ionic interactions may serve as a useful vehicle for the production of multilayer films via self-assembly can be inferred from Lee et al.[2] and Smotkin et al.[3]

(1) Ulman, A. *An Introduction to Ultrahigh Organic Films: From Langmuir-Blodgett to Self-Assembly*; Academic Press: Boston, 1991.

(2) Lee, H.; Kepley, L. J.; Hong, H.-G.; Mallouk, T. E. *J. Am. Chem. Soc.* **1988**, *110*, 618.

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Figure 1. Film thickness vs number of layers (determined by ellipsometry) for multilayers of I and II. The data are the average found for several different samples.

Figure 2. S 2p spectrum for a bilayer of ω-mercaptohexadecanoic acid illustrating the two overlapping S 2p doublets at 161.8 and 163.4 eV.

Utilizing this idea of forming a metal salt on a carboxylic acid surface, one could envisage that with a suitable choice of metal ions an alkanethiol monolayer could be chemisorbed on the carboxylic metal–salt surface. Such chemisorption should give noncentrosymmetric multilayer assemblies that are important for nonlinear optical applications.[4] We have therefore selected $HS(CH_2)_{10}COOH$ (I) and $HS(CH_2)_{15}COOH$ (II) as compounds for surface multilayer synthesis.[5]

Multilayer formation proceeds via the following fashion: In the first step, the gold substrate is exposed to a 1 mM solution of the ω-mercaptoalkanoic acid in ethanol (from 10 min to 4 h), producing a monolayer. After washing with ethanol and water, the thickness of the first monolayers was 14 and 18 Å for I and II, respectively, and both monolayers were completely wet by water ($\theta = 0°$). The surface was then exposed to a 1 mM solution of $Cu(ClO_4)_2$ in absolute ethanol (for 3 min), washed with ethanol, and then exposed to the thiol solution again. Repetition of the second and third steps led to a multilayer of the ω-mercaptoalkanoic acid. The addition of a new layer resulted in a completely water-wettable surface.

The formation of multilayers was monitored by both ellipsometry and grazing-angle FTIR spectroscopy. Figure 1 shows a plot of film thickness vs number of layers for multilayers of I and II.[6] The same linear behavior is observed when the FTIR reflection absorption spectrum is plotted vs number of layers for multilayers of I (Figure 1, supplementary material). The gradients in Figure 1 give the average increments in monolayer thicknesses of 14 and 16.5 Å for films I and II, respectively. Although films of only six layers have been shown in this communication, films of greater numbers of layers have now been prepared from II with the same linear behavior as shown in Figure 1. It is therefore believed that there is in principle no limitation to the total number of layers which may be deposited.[7]

In trying to understand the structure of these multilayers we have carried out careful XPS and FTIR studies. It was found that upon copper salt formation, the peak at 1719 cm⁻¹ associated with the –COOH group were replaced by a very strong peak at 1628 cm⁻¹, associated with the –COO⁻ group.[8] The addition of
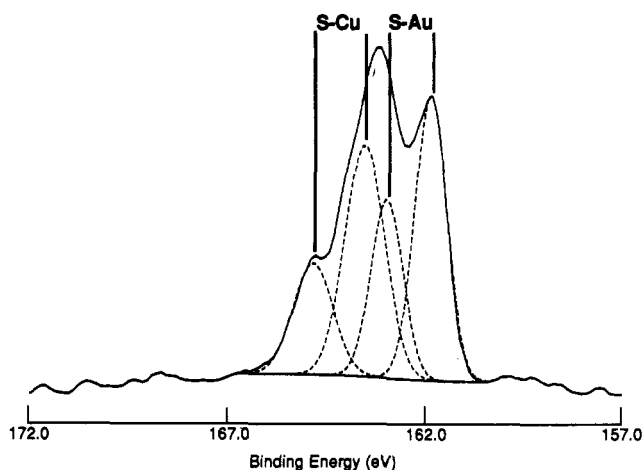
a second layer resulted in the replacement of the –COO⁻ peak by a broad peak at 1716 cm⁻¹. Further exposure of the two-layer system to the Cu^{2+} solution resulted in the reappearance of the strong 1628-cm⁻¹ peak, accompanied by a nearly complete disappearance of the 1716-cm⁻¹ peak.[9] The methylene stretch vibrations occurred at ca. 2919 and 2851 cm⁻¹ for the asymmetric and symmetric vibrations, respectively, in a sample of six monolayers of I. These showed decreasing FWHM values as the number of layers increased, going from 30 to 21.5 cm⁻¹ for $\nu_a(CH_2)$ and from 19 to 12 cm⁻¹ for $\nu_s(CH_2)$, between two and six layers of I, respectively. These shifts indicate a transformation from a "liquid-like" structure in the two-layer system to a "solid-like" structure in the six-monolayer sample. Both these peaks displayed high asymmetry.

Copper(II) is known to oxidize thiols to disulfides;[10] therefore, it was important to unambiguously determine the oxidation state of the copper. The XPS Cu $2p_{3/2}$ spectrum for a single layer of ω-mercaptohexadecanoic acid after exposure to 1 mM solution of $Cu(ClO_4)_2$ is characteristic of Cu^{2+} (Figure 2, supplementary material). The same spectrum is observed after the adsorption of a second ω-mercaptohexadecanoic acid layer. XPS also showed a shift of the CO_2 component of the C 1s peak from 289.4 eV in the free acid to 288.5 eV in the copper salt. The O 1s spectrum also changed from a two component doublet (532.4 and 533.9 eV), characteristic of an acid dimer of the free acid, to a narrow single component (531.9 eV) carboxylate-like structure in the copper salt. The XPS determined O/Cu stoichiometry of 4.5/1 also confirms the formation of a dimeric structure of the type (–$COO^-)_2Cu^{2+}$.[11]

A detailed literature search gave very few structures that contain both thiolate and carboxylate groups around a divalent metal ion.[13]
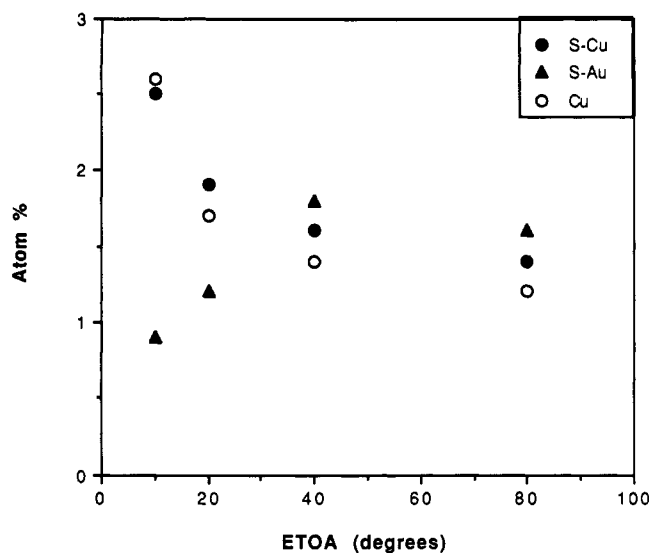
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(3) Smotkin, E. S.; Lee, C.; Bard, A. J.; Campion, A.; Fox, M. A.; Mallouk, T. E.; Webber, S. E.; White, J. M. *Chem. Phys. Lett.* **1988**, *152*, 265.

(4) Prasad, P. N.; Williams, D. J. *Introduction to Nonlinear Optical Effects in Molecules & Polymers*; Wiley Interscience: New York, 1991.

(5) Syntheses were carried out according to Bain, C. D.; Troughton, E. B.; Tao, Y.-T.; Evall, J.; Whitesides, G. M.; Nuzzo, R. G. *J. Am. Chem. Soc.* **1989**, *111*, 321.

(6) Film thicknesses were calculated with $n_f = 1.5$.

(7) The data reported in Figure 1 and Figure 1 in the supplementary material are of samples left in the thiol solution for 4 h; we believe that it will be possible to reduce this to a matter of minutes without significantly reducing the quality of the multilayer structures. This is because film thickness does not change for immersion times greater than 10 min.

(8) The $\nu_{as}(CO_2^-)$ appears at ~1610 cm⁻¹ in $(CH_3CO_2)_2Cu$. See: *The Coblentz Society Desk Book of Infrared Spectra*; Craver, C. D., Ed.; The Coblentz Society: Kirkwood, 1980. We note that the position of this peak varies with the metal ion as is apparent from IR spectra of LB films. For example, (Naselli, C.; Rabolt, J. F.; Swalen, J. D. *J. Chem. Phys.* **1985**, *82*, 2136) where $\nu_{as}(CO_2^-)$ appears at 1545 cm⁻¹ for the Cd^{2+} salt or (Kimura, F.; Umemura, J.; Takeaka, T. *Langmuir* **1986**, *2*, 96) where $\nu_{as}(CO_2^-)$ appears at 1577 cm⁻¹ for the Ca^{2+} salt or (Kamata, T.; Umemura, J.; Takenaka, T.; Takehara, K.; Isomura, K.; Taniguchi, H. J. *Mol. Struct.* **1990**, *240*, 187) where $\nu_{as}(CO_2^-)$ appears at 1603 cm⁻¹ for the Ba^{2+} salt.

(9) We have attempted to react the COOH surface with copper(I) triflate, in degassed ethanol, in a glovebox filled with He gas. XPS analysis of this surface gave the same copper content as for the copper(II) salt.

(10) Michaelis, L.; Schubert, M. P. *J. Am. Chem. Soc.* **1930**, *52*, 4418.

(11) We believe that the formation of a dimeric structure should be a general phenomena when divalent metal ions are used. Recent X-ray diffraction studies of the effects of Ca^{2+} and Cu^{2+} on Langmuir monolayers of heneicosanoic acid show the same structural trends in both cases.[12]

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Figure 3. Angle resolved XPS data for a bilayer of ω-mercapto-hexadecanoic acid. Note that S–Cu and Cu track each other in 1:1 ratio at all angles, suggesting their close proximity in the bilayer.

Usually, a thiolate is the preferred ligand, even when a carboxylate group is present,[13a,14] Furthermore, weakly bound short chain carboxylic acid species have been used in self-assembly to "protect" gold surfaces from unwanted adventitious contaminants. The acid is removed easily during the subsequent thiol adsorption. From angle-resolved XPS studies to determine whether there is any competitive adsorption between the carboxylate and the thiol functionalities on gold surfaces, we have found that there is, within the detectable limits, no carboxylate–substrate binding and that the thiolate–substrate reaction is dominant.[15] Finally, it has been found that the binding energies of alkanethiols to copper and to gold surfaces are similar.[16]

The structure emerging from the data presented so far is that multilayer formation occurs via the formation of copper(II) thiolate adsorbed on an acid surface. Figure 2 shows an XPS spectrum indicating the two types of sulfur species in the system, one bonded to gold (161.8 eV) and one to the Cu(II) (163.5 eV). We note that the interlayer bonding is not clear, however, given the surface stoichiometry, it is unlikely that we have a simple $-CO_2-Cu-S-$ connection. From the wetting data it is concluded that the ω-mercaptoalkanoic acid is attached to the copper carboxylate surface through the thiol end (the advancing contact angle on an SH surface is 71 ± 3°).[17] As a control reaction, we exposed the Cu^{2+} surface to a 1 mM solution of arachidic acid in an ethanol–dodecane mixture. No adsorption of the arachidic acid could be detected. Figure 3 presents the XPS as a function of electron takeoff angle (ETOA) for the two sulfur species and copper, clearly indicating that the second monolayer is adsorbed through the Cu–S bonding mode.[18] However, there are two disturbing points in Figure 3. The first is the S–Cu and Cu that track each other in 1:1 to 1.1:1 ratio at all angles, thus suggesting their close proximity in the bilayer, but in disagreement with an expected 2:1 ratio. Note that if the ratio of 1:1 is correct, the number of molecules in the second layer should be half of that in the first one, and so on. This sharp decrease in monolayer density is in complete disagreement with both the ellipsometric and the IR data. The second is that the angle-dependent XPS data are inconsistent with a structure in which the copper and the sulfur bound to it are buried beneath ~16 Å of hydrocarbon and may suggest a chemisorption of the carboxylic group on the Cu^{2+} surface. This, however, is in disagreement with the fact that

arachidic acid does not adsorb on these Cu^{2+} surfaces. Thus, while all evidence suggests the formation of complete monolayers, the XPS data suggest otherwise. We believe that complete monolayers are formed with thiol adsorption and with a 2:1 S/Cu ratio and that XPS is not a quantitative analytical tool in this case. A careful examination of many XPS spectra shows that even in the "best" cases, the Cu^{2+} peak is skewed, suggesting some reduction of the copper, even upon very short exposure to X-rays. Such reduction, for example to Cu^{1+}, results immediately in the formation of disulfides that would desorb in the ultrahigh vacuum, leaving a partial monolayer. If this is correct—we could not find any evidence in the XPS data to dispute it—both the S/Cu ratio and the takeoff angle results can be understood. Still, we cannot explain why we could not produce complete monolayers from simple alkanethiols (e.g., octadecanethiol $CH_3(CH_2)_{17}SH$) on the copper carboxylate surface. The only speculation we can provide is that since there is only one Cu^{2+} ion for two alkyl chains, the carboxylic groups play an important role in the adsorption, probably through H-bond stabilization of molecular dimers.

While full structural characterization of these films awaits detailed study, ellipsometry, XPS, and preliminary IR spectra indicate that water-stable multilayers of uniform thickness can be self-assembled via sequential adsorption of ω-mercaptoalkanoic acid and Cu^{2+} ions.

Supplementary Material Available: FTIR reflection absorption spectrum vs number of layers for multilayers of I and an XPS Cu $2p_{3/2}$ spectrum (2 pages). Ordering information is given on any current masthead page.

Kinetic, Thermodynamic, and Spectral Characterization of the Primary Cu–O₂ Adduct in a Reversibly Formed and Structurally Characterized Peroxo–Dicopper(II) Complex

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As a part of our continuing investigations of biomimetic Cu^I_n/O_2 reactivity,[2,3] we recently described the reversible reaction of the mononuclear cuprous complex $[LCu(RCN)]^+$ (**1**, L = tris[2-pyridyl)methyl]amine, R = CH_3 or C_2H_5) with O_2 to give the trans-μ-1,2-peroxo-bridged dicopper(II) complex, $[\{LCu\}_2(O_2)]^{2+}$ (**3**) (Cu⋯Cu = 4.36 Å).[2a] Copper–dioxygen interactions are of fundamental importance in Cu(I) autoxidation and chemical/biological oxidation processes.[4–6] One-to-one Cu–O₂ adducts are implicated in these processes, while recent studies reveal the presence of such entities as important intermediates in the action of copper phenylalanine hydroxylase[7] and amine oxidases.[8]

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(16) Nuzzo, R. G., private communication.
(17) Balachander, N.; Sukenik, C. N. *Langmuir* **1990**, *6*, 1621.
(18) Long exposure of samples to X-rays results in the apparent reduction of the Cu(II) and disorption of material. Therefore, it is recommended to use a new sample for every takeoff angle.

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