Photopatterning Hot Paper

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Direct UV-Induced Functionalization of Surface Hydroxy Groups by Thiol–Ol Chemistry**

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Abstract: *A novel UV-initiated surface modification method for the direct functionalization of surface hydroxy groups with thiol-containing molecules (termed "thiol–ol" modification) is described. This method is based on the oxidative conjugation of thiols to hydroxy groups. We demonstrate that different thiol-containing molecules, such as fluorophores, thiol-terminated poly(ethylene glycol) (PEG-SH), and a cysteine-containing peptide, can be attached onto the surface of porous poly(2-hydroxyethyl methacrylate-co-ethylene dimethacrylate). Direct functionalization of other hydroxy-group-bearing surfaces, fabrication of micropatterns, and double patterning have been also demonstrated using the thiol–ol method.*

The control of surface properties, such as hydrophobicity and hydrophilicity,[1] is crucial in most of the research and industrial applications where surfaces are present. To achieve desired surface properties, different methods of surface modification, such as chemical vapor deposition,[2] electron beam polymerization,[3] plasma treatment,[4] and photografting,[5] have been commonly used. Recently, a number of strategies for light-induced surface functionalization, based on, for example, thiol–alkyne/alkene chemistry,[6] the Diels–Alder reaction,[7] tetrazole–ene chemistry,[8] alkyne–azide chemistry,[9] oxime ligation,[10] hydrosilylation,[11] and photolytic decomposition of perfluoroarylazides,[12] have been developed. One of the primary advantages of all light-initiated techniques is that they can be used to fabricate functionally patterned surfaces.[5a,d] However, the existing methods are restricted to only a few types of chemical reactions, and some methods, such as photografting,[5] require oxygen-free conditions. In addition, the type of surface functional groups that can be modified using light-induced reactions is limited. To our knowledge, although the hydroxy group is one of the most common surface functionalities, there are no methods for the direct photoinduced modification of hydroxy-functionalized surfaces.

Here, we describe a UV-initiated surface modification method for the functionalization of surface hydroxy groups by reaction with thiol-containing molecules. Unlike the UV-initiated radical additions, such as thiol–ene[13] and thiol–yne chemistry,[6a,14] our approach is based on an oxidative conjugation of thiols to hydroxy groups present on the surface (Figure 1; termed thiol–ol chemistry). We show that this reaction requires oxygen during UV irradiation, thereby making surface modification under air possible. In addition, this method of surface modification is simple and initiator-free. The reaction is characterized using time-of-flight secondary-ion mass spectrometry (ToF-SIMS), X-ray photoelectron spectroscopy (XPS), water contact-angle measurements, and electrospray ionization mass spectrometry (ESI-MS). The approach is demonstrated by modification of two model

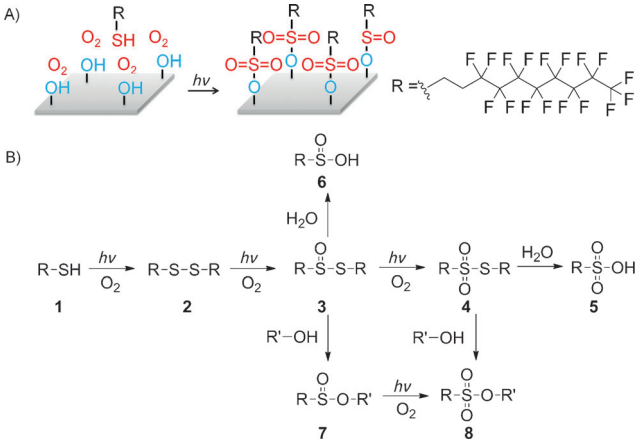

Figure 1. A) Representation of surface modification by thiol–ol chemistry under UV irradiation. The hydrophilic surface of HEMA-EDMA was coated with a layer of **1** and irradiated with UV light under air for 30 min. This leads to the oxidative conjugation of the thiols with surface hydroxy groups through the formation of sulfonic and sulfinic esters. B) Possible mechanism of the functionalization of surface hydroxy groups by thiol–ol chemistry mediated by oxygen and UV irradiation.

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hydroxy-functionalized surfaces: poly(2-hydroxyethyl methacrylate-*co*-ethylene dimethacrylate) (HEMA-EDMA) and a cellulose membrane. We demonstrate that thiol-containing fluorophores (FITC-SH (FITC = fluorescein isothiocyanate), Rhodamine-SH), polymers (PEG-SH), and peptides (FITC-β-Ala-GGGGC) can be used to functionalize hydroxy-terminated surfaces.

It has been known that thiols and disulfides can be converted into the corresponding sulfonic acids upon UV irradiation in the presence of oxygen.[15] During UV irradiation, stable intermediates, such as thiosulfinates and thiosulfonates, are produced.[15b] Moreover, it was reported that in the presence of alcohols, sulfinic and sulfonic esters could be formed in parallel with thiosulfonate and thiosulfinate.[15a] We hypothesized that thiols could be oxidized and covalently conjugated to surface hydroxy groups under UV light in the presence of oxygen (Figure 1).

The thiol–ol reaction was first demonstrated by functionalization of a thin, hydrophilic HEMA-EDMA layer with alkyl thiols. The hydrophilic HEMA-EDMA layers were prepared by in situ free-radical polymerization as described previously.[5i,16] Alkyl thiols of different lengths were dissolved in acetone (50% v/v), and applied to the HEMA-EDMA surface, which was then irradiated with UV light in air for 30 min (260 nm, 12 mW cm^{-2}). During the irradiation, the surface dried completely and a solid thin film was formed on the HEMA-EDMA surface. The modified HEMA-EDMA substrates were then washed three times with acetone and methanol, which completely removed the initially formed solid film. The static water contact angle (WCA) changed from 37° to 63° after the modification with 1-butanethiol. The hydrophobicity of the modified thin layers gradually increased with the increase of the length of the alkyl thiols used for the modification (Figure S1 in the Supporting Information (SI)). When 1*H*,1*H*,2*H*,2*H*-perfluoro-1-decanethiol was used to modify the HEMA-EDMA thin layer, a highly hydrophobic surface (static WCA of ca. 130°) was obtained. The stability experiment (Figures S2 and S3 (SI)) indicates that the surface modification was not caused by simple physisorption of the thiols. The modified surfaces were also stable under both mild acidic or basic conditions (Figure S3 (SI)).

According to the hypothesized mechanism of the thiol–ol surface modification (Figure 1B), the first step is the oxidation of thiols (**1**) to disulfides (**2**). The disulfides can be further oxidized to thiosulfinates (**3**) and thiosulfonates (**4**), which can either be hydrolyzed to sulfinic (**6**) and sulfonic (**5**) acids, or react with an alcohol to produce sulfinic (**7**) and sulfonic (**8**) esters, respectively. In order to prove this hypothesis, we tested whether a disulfide could be used to modify a surface bearing hydroxy groups under UV irradiation. A HEMA-EDMA thin layer was doped with a dibutyl disulfide solution (50% v/v in acetone) or 1-butanethiol solution (50% v/v in acetone) and irradiated with UV light for 30 min in the presence of oxygen. The same experiment was performed in the dark under air as well as under UV irradiation but in the absence of oxygen. The WCAs of both HEMA-EDMA surfaces modified by dibutyl disulfide and 1-butanethiol under UV and in the presence of air increased from 37° to roughly 63° (Figure S4 (SI)). However, no change of WCAs was observed for the samples prepared in the dark or in the absence of oxygen. These results indicate that both the dibutyl disulfide and 1-butanethiol can be used for the UV-initiated modification of surface hydroxy groups and that oxygen is required for the modification.

The surface morphology was characterized by scanning electron microscopy (SEM). Figure 2A shows that the morphology of the HEMA-EDMA thin layer did not

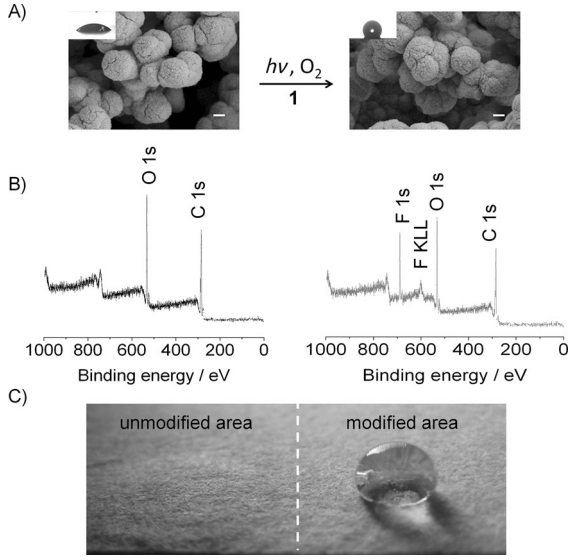

Figure 2. Functionalization of a hydrophilic HEMA-EDMA thin layer and a cellulose membrane with the perfluorinated alkyl thiol **1** by thiol–ol chemistry. 1*H*,1*H*,2*H*,2*H*-Perfluoro-1-decanesulfonic ester is formed by the oxidative conjugation with hydroxy groups on the HEMA-EDMA surface. A) SEM images (inserts: water droplets on the corresponding surfaces); scale bars: 200 nm. B) XPS spectra of the unmodified (left) and modified surfaces (right). C) Water droplets on the unmodified (left) and modified (right) cellulose membrane (blotting paper).

change after grafting with **1**. X-ray photoelectron spectroscopy (XPS) confirmed the presence of F 1S and F KLL peaks after modification of the HEMA-EDMA surface with **1** (Figure 2B and Figure S5 (SI)). To further confirm the covalent binding of the thiols to the surface, time-of-flight secondary-ion mass spectrometry (ToF-SIMS) was used. A series of fragments, such as $CF_3(CF_2)_7CH_2CH_2SO_3CH_2^-$, $CF_3(CF_2)_7CH_2CH_2SO_3^-$, $CF_3(CF_2)_7CH_2CH_2SO_2CH_2^-$, and $CF_3(CF_2)_7CH_2CH_2SO_2^-$ were observed only on the HEMA-EDMA surface modified with **1** ($CF_3(CF_2)_7CH_2CH_2SH$) (Figure 3). The assignment, possible structure, and intensity of the fragments are shown in Table S1 (SI). The calculated and observed isotopic abundance ratios of $CF_3(CF_2)_7CH_2CH_2SO_3^-$ and $CF_3(CF_2)_7CH_2CH_2SO_2^-$ are shown in Figure S6 (SI). A slight excess of $[M+H]^-$ fragments is seen. The determined masses of the described fragments and the observed isotopic patterns are in good agreement with the given chemical assignments. The presence of peaks for $CF_3(CF_2)_7CH_2CH_2SO_3CH_2^-$ and $CF_3(CF_2)_7CH_2CH_2SO_2CH_2^-$ support the oxidative esterification of thiol **1** with the surface

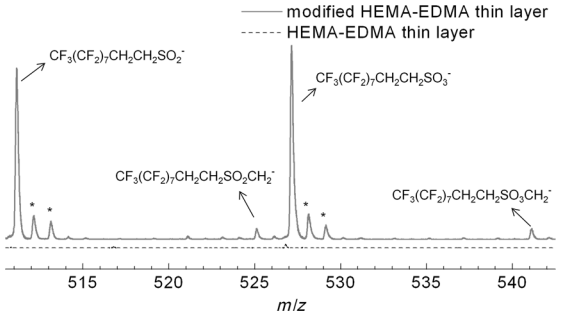

Figure 3. ToF-SIMS spectra of HEMA-EDMA thin layers before (black) and after (red) modification with the perfluoroalkylthiol **1**, negative mode. The spectrum shows peaks of sulfonic and sulfinic esters derived from **1** conjugated to the surface hydroxyethyl groups, $CF_3(CF_2)_7CH_2CH_2SO_3CH_2^-$, $CF_3(CF_2)_7CH_2CH_2SO_3^-$, $CF_3(CF_2)_7CH_2CH_2SO_2CH_2^-$, and $CF_3(CF_2)_7CH_2CH_2SO_2^-$. Isotopic peaks are marked with asterisks.

hydroxyethyl groups, which was the only source of HO-CH_2 groups available during the UV irradiation (Figure 1 A). To verify the formation of sulfonic and sulfinic esters in solution in the presence of an alcohol, we irradiated solutions of 1-butanethiol in ethanol or acetone; the products were collected immediately after irradiation and analyzed using electrospray ionization mass spectrometry (ESI-MS). We observed the corresponding signals of ethyl butane-1-sulfinate and ethyl butane-1-sulfonate only for the sample prepared with the ethanol solution (Figures S7 and S8 (SI)), confirming the thiol–ol reaction in solution. However, different side products, such as 1-butanesulfinic acid, 1-butanesulfonic acid, sulfuric acid, and 1-(butylsulfinyl)butane, were observed.[15a,17] Because of the possible side reactions, thiol–ol chemistry may not be suitable for the synthesis of sulfinic and sulfonic esters in solution. However, when the reaction is conducted on a surface, no side products are grafted. Thus, this phototriggered conjugation technique could be a useful method for the direct modification and patterning of hydroxy-functionalized surfaces.

The main advantage of all photoinitiated grafting methods is that 2D patterns of surface functional groups can be created by applying a photomask. In this work, we prepared different types of surface patterns by direct UV-triggered functionalization of surface hydroxy groups by means of the thiol–ol reaction (Figure 4 A). Hydrophilic–hydrophobic micropatterns on the HEMA-EDMA surface were prepared by covering the surface with a solution of hydrophobic thiol **1** in acetone, followed by UV irradiation through a photomask for 30 min. After irradiation, the mask was removed and the surface was washed with methanol and acetone three times and dried. This modification resulted in the formation of a hydrophobic grid where the surface was irradiated with UV light, while the nonirradiated parts were left hydrophilic (Figure 4 A,C). The produced micropattern was characterized by ToF-SIMS (Figure 4 B and Figure S9 (SI)), showing a clear pattern of squares and a good contrast of the SO_2^-, SO_3^-, $CF_3(CF_2)_7CH_2CH_2SO_2^-$, $CF_3(CF_2)_7CH_2CH_2SO_3^-$, F_2^-, and CF_3^- ions between the irradiated and nonirradiated areas (Figure 4 B and Figure S9 (SI)). Figure 4 C shows an example of the patterning of different liquids using the produced hydrophilic–hydrophobic pattern. We also tested the behavior of fluorescent Hela-eGFP cells on the patterned HEMA-EDMA surface. Hela-eGFP cells were seeded on the patterned surface and incubated for 48 h. Figure S10 (SI) shows that the hydrophilic squares on the patterned surface were populated by the cells, while the hydrophobic barriers (indicated by dashed lines on the micrograph) were significantly less occupied. The preferential adhesion of the cells was also confirmed by growing cells on nonpatterned unmodified and modified HEMA-EDMA surfaces. After incubation for 48 and 72 h, the cell population on the unmodified hydrophilic surface was 30 times greater than that on the modified hydrophobic surface, which correlates with our previous cell studies on fluorinated porous polymer surfaces (Figure S11 (SI)).[5i,16]

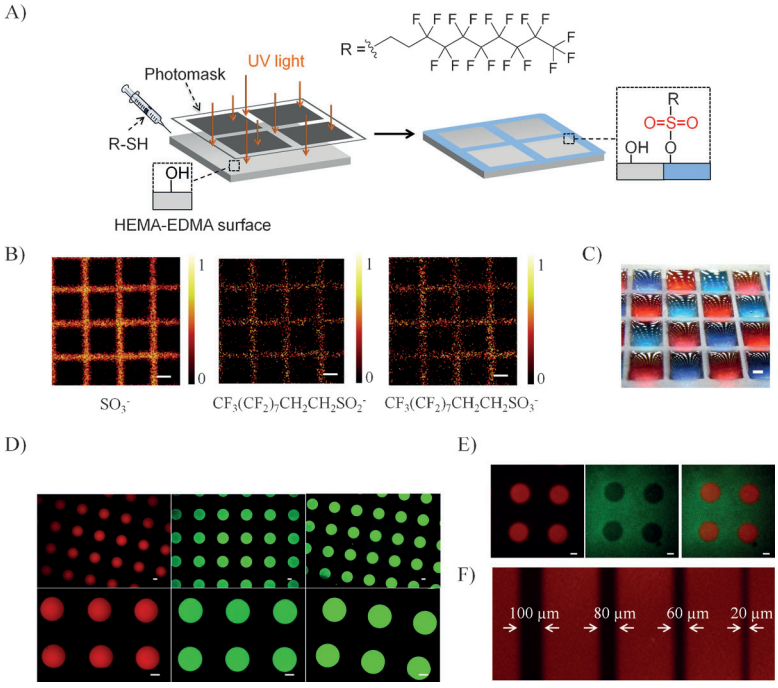

Figure 4. A) Representation of the micropattern fabrication. B) ToF-SIMS images (SO_3^-, $CF_3(CF_2)_7CH_2CH_2SO_2^-$, and $CF_3(CF_2)_7CH_2CH_2SO_3^-$ ions, negative mode) of the HEMA-EDMA thin layer patterned with **1**; scale bars: 400 µm. C) Photograph of colored water droplets on the hydrophilic–hydrophobic micropattern prepared by patterning **1** on the hydrophilic HEMA-EDMA surface; scale bar: 1 mm. D) Fluorescence microscope images of the nanoporous HEMA-EDMA surfaces (on glass plate) modified with Rhodamine-SH (red, left), FITC-SH (green, middle), and FITC-peptide-SH (Fluorescein-β-Ala-GGGGC, green, right); scale bars: 500 µm. E) Fluorescence microscope images of consecutive double patterning on a macroporous HEMA-EDMA surface (on glass plate) with Rhodamine-SH (red, left) and FITC-SH (green, middle), and merged pattern (right); scale bars : 500 µm. F) Fluorescence microscope image of Rhodamine-SH pattern on the nanoporous HEMA-EDMA surface (on glass plate) with lines of different widths.

Thiol-containing fluorophores, Rhodamine-SH and FITC-SH, could be also conjugated to the nanoporous HEMA-EDMA surface as shown in Figure 4D and Figure S13 (SI). Surface patterning often requires the sequential functionalization of a surface with multiple chemical moieties to create multifunctional surfaces. In order to show that thiol–ol chemistry is compatible with such sequential patterning, a macroporous HEMA-EDMA layer was first modified with Rhodamine-SH through a photomask; then the whole surface was treated with a FITC-SH solution and irradiated. The results clearly show that the hydroxy groups exposed to UV light in the first step were modified with Rhodamine, while the irradiation of the whole surface in the second step functionalized the remaining hydroxy groups to create a double-colored Rhodamine–FITC micropattern (Figure 4E and Figure S14 (SI)). With this photopatterning method, a micropattern with a resolution of 20 μm could be fabricated (Figure 4F). To investigate the depth of the thiol–ol modification, Rhodamine-SH was used to create a micropattern on a 45 μm-thick macroporous HEMA-EDMA polymer film. The depth of the thiol–ol modification, determined from the 3D reconstruction of confocal fluorescence microscope images, was approximately 40 μm (Figure S12 (SI)), confirming that the reaction occurs throughout the whole thickness of the porous polymer.

The ability to functionalize surfaces with biomolecules and polymers is important for many applications. To demonstrate the versatility of the thiol–ol method, FITC-peptide-SH (Fluorescein-β-Ala-GGGGC) was conjugated to the nanoporous HEMA-EDMA surface by UV irradiation. Figure 4D (right) and Figure S13 (SI) show clear patterns of the immobilized peptide. Due to the abundance of the thiol group in different biomolecules, the thiol–ol modification method has the potential to become practical for the surface immobilization of biomolecules. Moreover, thiol-terminated polyethylene glycol (PEG-SH, $M_w = 5000\ g\,mol^{-1}$), was immobilized onto a HEMA-EDMA thin layer through UV irradiation, which was confirmed by ToF-SIMS measurements (Figure S15 (SI)). The produced micropattern showed a clear pattern of squares and a good contrast of the S^-, $C_2HO_2^-$, $C_4H_9O_3^-$, $C_3H_5O^-$, and $C_2H_5O^-$ ions between irradiated and nonirradiated areas (Figure S15 (SI).

Finally, to show that the thiol–ol method is compatible with another hydroxy-containing substrate, a cellulose-based membrane (blotting paper) was wetted with a mixture of the fluorinated thiol **1** in acetone (50% v/v), and then irradiated with UV (260 nm, $12\ mW\,cm^{-2}$) for 30 min under air. After washing, the area irradiated with UV became highly hydrophobic (Figure 2C, Video S1 (SI)). There was no visual difference between the modified and unmodified areas. The change in surface wettability demonstrated the applicability of the thiol–ol reaction for the direct immobilization of thiols to another important type of materials, paper.

In conclusion, we have presented a photochemical method for the direct functionalization of surface hydroxy groups with thiol-containing compounds. This photoinduced conjugation based on the oxidative esterification leads to the formation of sulfinic and sulfonic esters on the hydroxy-functionalized surfaces as confirmed by ToF-SIMS and XPS. We demonstrated that different thiol-containing molecules, including fluorophores, PEG, and a peptide, could be photopatterned using this method. UV-initiated surface modification is crucial in a variety of research and industrial fields, especially for creating different types of surface patterns. However, to our knowledge, there are no other photochemical methods that allow for the direct functionalization of surface hydroxy groups, although substrates with exposed hydroxy groups are among the most common materials. Therefore, the presented method can be useful in all applications where the direct photochemical modification or patterning of hydroxy-functionalized surfaces without additional intermediate steps is important.

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