

Method Section:

The data bases taken as the basis were:

- *DNP*: Dictionary of Natural Products on CD-ROM (Chapman&Hall), 78318 structural entries (status: June 96)
- *BNPD*: Bioactive Natural Product Database, Szenzor Management Consulting Company, Budapest, (Hungary) (by Berdy), 29432 entries of natural products with described biological activity (status: July 96)
- *Drugs*: Pharmaceutical products/compounds in development recorded in Pharmaprojects, RDFocus and in the active compounds pool of Bayer AG, 14596 entries (status: June 96)
- *ACD*: Available Chemicals Directory, Version 93.2, from Molecular Design Ltd. Information Systems Inc., San Leandro, CA (USA), 182822 entries
- *Synthetics*: Representative pool of synthetic test compounds from Bayer AG.

The construction of the data bases unavoidably resulted in some peculiarities in the data evaluation, which should be noticed in the detailed inspection of the determined results: *DNP* contains 78318 compounds from which however only 70450 appear as authentic natural products. In some cases it became necessary to use both data sets as a consequence of the restraints applied. *DNP* does not include any identifier for natural product sources, so that an evaluation of producer organisms was limited on *BNPD*. The numbers of investigated compounds in the figures are lower than the total numbers given in the data bases as the data sets are partly incomplete. For a clearer and simplified description only parts of selected data bases are compared in the tables and figures. The data bases were converted in MACCS-^[3] and UNITY^[4]-format and analyzed with the available default methods for the evaluations related to structures. The structural similarity analysis between molecules was obtained from the 2D-fingerprint descriptors in the standard definition of UNITY.^[4] The similarity/dissimilarity between pairs of molecules was calculated according to Tanimoto^[5] and discussed in reference to a limiting value of 0.75. The analysis of pharmacophoric groups, predefined from a general chemical understanding, was carried out with software developed by Bayer AG. Full details can be found in the supporting information.

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Surface-Initiated Polymerization for Amplification of Self-Assembled Monolayers Patterned by Microcontact Printing**

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The generation of complex patterns in polymer films is traditionally achieved by combining spin-casting and photolithographic techniques.^[1] Polymer films patterned by this procedure are widely used for the fabrication of microelectronic devices^[2] or as selective barriers to etchants^[3] and redox-active probes.^[4] While successful, the usefulness of these patterned polymer films is restricted by their limited stability with respect to solvents and their tendency to undergo subsequent chemical reactions^[5] as well as by difficulties in their preparation over large areas and complicated topographies.^[6] To address these latter challenges, Whitesides and co-workers have introduced the concept of microcontact printing (μ CP)^[7] for the preparation of patterned self-assembled monolayers (SAMs) on both planar and curved surfaces.^[8] Self-assembled monolayers formed from alkanethiols on gold and silver have been used as barriers to wet chemical etchants.^[9] In this approach, however, the usefulness of SAMs as barriers to etchants is compromised by the susceptibility of monolayer films to formation of defects,^[10] their lack of barrier properties when using dry etchants such as reactive ions, and the conflicting time scales necessary for complete formation of SAMs and for high-resolution patterning.^[11] To address these limitations, we report a first step in a program of research aimed at using polymerization as a tool for chemically amplifying surfaces patterned with organic molecules by microcontact printing into patterned polymer brushes.^[12] The preparation of a macromolecular barrier instead of a molecular one provides a means to mask defects within monolayers and to introduce resistance to a wide range of etchants. We also believe it can provide an avenue to high-resolution patterning of polymers through surface-initiated polymerization to mask incomplete regions of SAMs formed rapidly so as to minimize lateral transport of thiols. The work we report here also represents a general methodology for patterning polymeric films on surfaces.

The basic strategy of this novel process is depicted in Figure 1. Initially a nonreactive SAM formed from CH₃-

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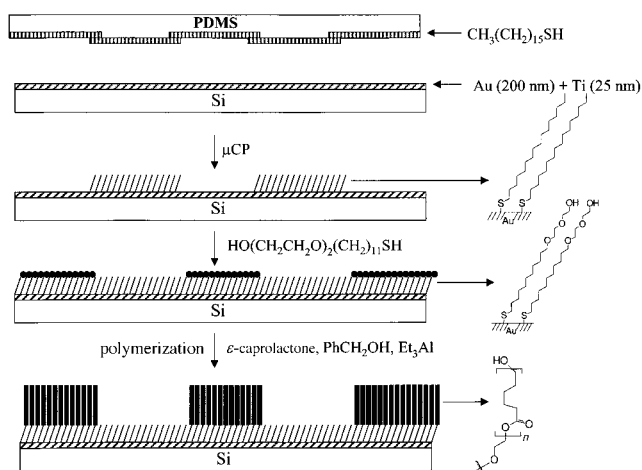


Figure 1. Scheme of strategy for amplification of a patterned SAM prepared by microcontact printing into a patterned polymer brush.

$(\text{CH}_2)_{15}\text{SH}$ is microcontact printed onto a gold surface by standard techniques.^[7] A second functionalized thiol, in this case $\text{HO}(\text{CH}_2\text{CH}_2\text{O})_2(\text{CH}_2)_{11}\text{SH}$ (**1**), is then selectively assembled onto the bare regions of the gold surface by simple immersion into a solution of the functionalized thiol. This procedure results in the formation of a surface patterned with regions of hydroxyl group functionalized SAMs and regions of nonfunctionalized SAMs.^[13] The pattern generated by this technique is, therefore, a direct representation of the original poly(dimethylsiloxane) (PDMS) stamp with the functionalized areas representing a negative image. The selection of the alkanethiol with a terminal di(ethylene glycol) group (**1**) as the initiating moiety was governed by our attempts to use simpler functionalized thiols such as $\text{HO}(\text{CH}_2)_{11}\text{SH}$ (**2**). We observed the surface properties of SAMs formed from **2** to change rapidly with time (Figure 2), and we found these surfaces to be unreliable for the growth of polymers.^[14] In contrast, the surface properties of SAMs formed from **1** were stable over extended periods and provided a highly reliable and reproducible route for the synthesis of hydroxyl group functionalized surfaces.

The final step in this strategy is the surface-initiated ring-opening polymerization (ROP) of ϵ -caprolactone from the functionalized areas of the patterned SAM. The incorporation of reactive hydroxyl groups permits the direct use of these groups, since they are known to be effective initiators for the

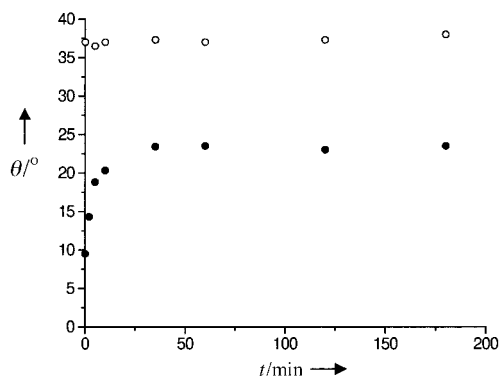


Figure 2. Advancing contact angles of water θ measured as a function of time t on SAMs from **1** (○) or **2** (●).

ROP of cyclic esters such as lactones and lactides in the presence of a suitable organometallic promoter such as aluminum alkoxides.^[15] Initial experiments involved the addition of triethylaluminum to the hydroxyl group containing patterned SAMs followed by addition of ϵ -caprolactone. This procedure resulted in either uncontrolled growth of polymer from the surface or in destruction of the patterned surface. Presumably this is due to the extremely low concentration of initiating sites on the patterned substrate, which leads to susceptibility to trace impurities. Furthermore, extremely large molar ratios of ϵ -caprolactone to the initiating sites leads to no control over the degree of polymerization of the chains grown from the surface. To overcome these difficulties, it was necessary to add a predetermined amount of “free” initiator such as benzyl alcohol to the reaction mixture. Dynamic exchange between the added free initiator and the surface-bound initiators mediates the polymerization, and therefore permits control of the degree of polymerization and thickness of the chains grown from the surface.^[16] This modified procedure resulted in the controlled growth of patterned polymer brushes in less than three hours at 25–30 °C. As can be seen in Figure 3, the thickness of the

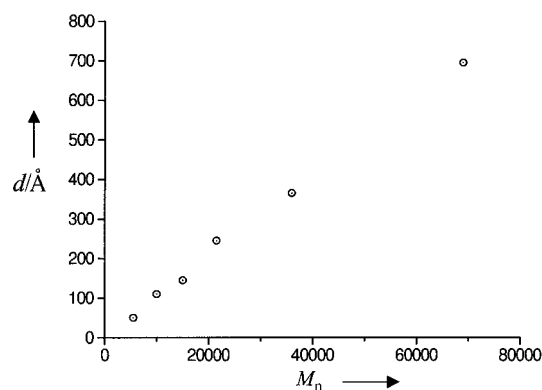


Figure 3. Ellipsometric thicknesses d of brushes of poly(caprolactone) measured as a function of the number-averaged molecular weight M_n of the free polymer formed from the added initiator.

poly(caprolactone) film is a linear function of the degree of polymerization of the polymer formed in solution from the free initiator. The degree of polymerization of the polymer formed in solution is in turn dictated by the initial ratio of benzyl alcohol to caprolactone.^[17] The “soluble” poly(caprolactone) was removed by repeated washing of the gold wafer with toluene and dichloromethane.

Chemical amplification of the patterned hydroxyl group functionalized SAM into spatially localized polymer brushes was confirmed by atomic force microscopy (AFM, Figure 4). The regions of the surface presenting hydroxyl groups were covered by continuous polymer films. Thicknesses of polymer films estimated from AFM images were in close agreement with those measured by ellipsometry. For example, a brush measured to have a thickness of 28 ± 4 nm by AFM was determined to have an ellipsometric thickness of 27 ± 3 nm. High-resolution AFM images reveal internal structure within the polymer films, which may reflect the semicrystalline nature of the poly(caprolactone) brushes.

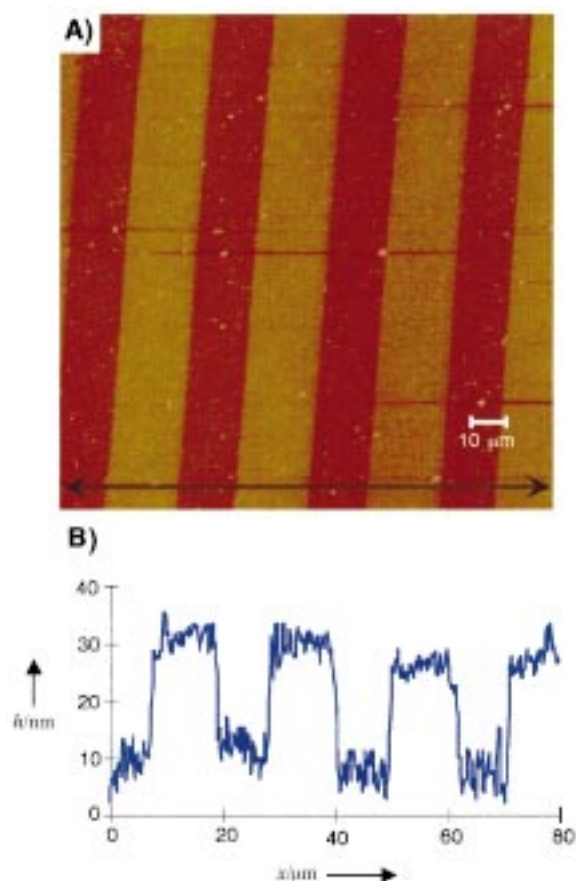


Figure 4. A) Low-resolution contact AFM image and B) cross-sectional profile of patterned brushes formed from poly(ϵ -caprolactone); h = height of the polymer brush, x = pattern position. The location of the cross-sectional profile is marked in (A) by the double-headed arrow.

In conclusion, we have demonstrated a novel strategy for the preparation of patterned polymer brushes from microcontact printed gold surfaces. The key feature of this approach is the use of surface-initiated polymerization to chemically amplify the patterned SAM into a macromolecular film. This methodology not only leads to formation of patterned polymeric thin films without the need for expensive photolithographic tools, but also uses SAMs in a way that should be tolerant to imperfections within the original monolayer structure. Extension of this strategy to other living and controlled polymerization systems, as well as exploration of the etch and barrier resistance properties of these novel thin films, are under investigation.

Experimental Section

Materials and substrates: Gold films (200 nm) were deposited by electron beam evaporation on glass slides that had been primed with titanium (10–25 nm) to promote adhesion between the glass and gold. The elastomeric stamp was formed by pouring a mixture of PDMS prepolymer and its curing agent Sylgard 184CA (10/1 w/w) onto a clean polystyrene Petri dish. The dish was left at 60 °C for at least 12 h to ensure a complete cure of the polymer mixture. After removal of the master, the elastomeric stamp was rinsed three times with ethanol and dried under a flow of N₂ for 30 s. The thiol derivatives were prepared according to Whitesides et al.^[10]

Microcontact printing: A solution of 3 mM hexadecanethiol in ethanol was used as the ink. The stamp was inked by brushing its surface with a cotton swab soaked in the inking solution. The excess solvent was evaporated from

the stamp by placement of the stamp under a stream of N₂ for 30 s. The stamp was placed by hand onto a polycrystalline gold substrate and withdrawn after a contact period of about 5 s. The stamped gold substrate was washed with ethanol, dried under a flow of N₂ for 30 s, and immersed into a 1 mM solution of **1** in ethanol for 30 min. The slides were then washed with ethanol and dried under a flow of N₂.

Polymerization: The diethylaluminum alkoxides were prepared in a glove box purged with argon. To a solution of benzyl alcohol (103 μ L, 1.0 mmol) in dry toluene (15 mL) was added dropwise triethylaluminum (0.55 mL of a 2.0 M solution, 1.1 equiv, 1.1 mmol). This solution was vigorously stirred at room temperature for 30 min. Gold films supporting either SAMs formed from **1** or patterned SAMs formed from **1** and hexadecanethiol were then placed into the solution and allowed to stand for 1 h before the toluene was removed under vacuum. Dry toluene (75 mL) was then added followed by ϵ -caprolactone (11.1 mL, 100 mmol), and the polymerization mixture stirred at room temperature for 3 h. To the viscous solution was added acetic acid (5 mL). After the mixture was stirred for 5 min, the gold wafers were removed and washed repeatedly with dichloromethane, toluene, THF, and ethanol. To measure the molecular weight and polydispersity of the polymer grown in solution, the supernatant from the polymerization mixture was precipitated into methanol (500 mL), collected by precipitation, and dried. The polydispersity of these materials were typically between 1.2 and 1.4, and the molecular weights were within 10% of the theoretical value.

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