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Backbone-Degradable Polymers *via* Chemical Vapor Deposition

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Abstract: Polymers prepared by chemical vapor deposition (CVD) polymerization have found broad acceptance in research and industrial applications. However, their intrinsic lack of degradability has limited wider applicability in many areas, such as biomedical devices or regenerative medicine. In this study, we demonstrate, for the first time, a backbone-degradable polymer directly synthesized *via* chemical vapor deposition (CVD). The CVD co-polymerization of [2.2]paracyclophanes with cyclic ketene acetals, specifically 5,6-benzo-2-methylene-1,3-dioxepane (BMDO), results in well-defined, hydrolytically degradable polymers, as confirmed by FTIR spectroscopy and ellipsometry. The degradation kinetics are dependent on the ratio of ketene acetals versus [2.2]paracyclophanes as well as the hydrophobicity of the films. These novel polymer coatings address a significant unmet need in the biomedical polymer field, as they provide access to a wide range of reactive polymer coatings that combine interfacial multifunctionality with degradability.

The medical field has increasingly witnessed a shift from permanent implant materials to biodegradable materials that degrade after their intended use.[1-2] For instance, surgical sutures,[3] controlled drug delivery systems,[4] drug-eluding stent coatings[5] or tissue engineering scaffolds[6] all benefit from degradable polymers. There exists numerous examples, where surface modification of biodegradable materials is required to introduce functional groups as anchor sites for biomolecule/drug conjugation.[7-9] To date, substrate-independent and widely applicable chemical vapor deposition (CVD) coatings are well established for non-degradable substrates (e.g., metals), but functional, degradable coatings remain illusive. For example, CVD polymerization of [2.2]paracyclophanes can yield versatile poly(*p*-xylylene) coatings, which have been successfully applied for a wide range of permanently implanted devices (*e.g.*, stents, pacemakers, or neural probes).[10] Some of these polymers are commercially available and the most widely used member of the family, also know as Parylene C, is an ISO 10993 and United States Pharmacopeia (USP) Class VI (highest biocompatibility class) material. Because of their unique processing through vapor phase polymerization, these polymers feature a range of advantages, such as low-temperature deposition, substrate-independency, absence of process solvents, high conformity, and excellent mechanical properties.[10-11] CVD-based poly(*p*-xylylene)s have also been synthesized displaying a wide range of reactive side groups for efficient bioconjugation.[12-13] While CVD polymers are widely used for functionalization of permanent implants and devices, they are intrinsically not degradable due to the absence of hydrolytically cleavable bonds in their backbone.[14]

Directly addressing this unmet need, we now report a novel class of functionalizable, and hydrolytically degradable polymer coatings made by chemical vapor deposition polymerization. Specifically, we use CVD co-polymerization to prepare degradable co-polymers displaying no functional group (co-polymer 2), hydroxyl groups (co-polymer 1) and alkyne groups (co-polymer 3) for further surface modification. Co-polymerization of functionalized [2.2]paracyclophanes with cyclic ketene acetal (CKA) molecules results in degradable ester linkages inserted into the all-carbon-based poly-*p*-xylylene backbone. CKAs fulfill two critical criteria in this context: (i) CKAs polymerize following a radical polymerization mechanism compatible with the CVD polymerization process, while undergoing a rearrangement that can insert ester bonds in the polymer backbone.[15-17] (ii) CKAs can sublime under the typical conditions required for CVD polymerization of [2.2]paracyclophanes.

While a range of different CKAs preferentially undergo ring-opening polymerization,[15] we focused on 5,6-benzo-2-methylene-1,3-dioxepane (BDMO), which was synthesized following a slightly modified literature-known procedure.[18-20] BMDO features a seven-membered cyclic ketene acetal ring, which has previously been shown to undergo quantitative rearrangement in solution-based reactions.[18, 21] The radical that is generated after rearrangement of BMDO is stabilized by the adjacent benzene ring (Scheme 1), which makes it particularly suitable for CVD polymerization.

For CVD co-polymerization, BMDO and [2.2]paracyclophanes, which act as the radical initiators, were sublimed at 0.07 Torr and temperatures above 100 °C and transferred in a stream of argon carrier gas into the pyrolysis zone, which was maintained at a temperature of 530 °C. After formation of the active intermediates (Scheme 1), the vapor was transferred into the deposition chamber, with the chamber wall temperature set to 120 °C and the holder cooled to 15 °C to optimize the deposition. Under these conditions, BMDO underwent molecular rearrangement followed by subsequent co-polymerization with the xylylene moieties. The co-polymerization proceeded with a growth rate of 0.1~0.2 Å/s and resulted in well-defined polymers displaying ester bonds in their polymer backbone.

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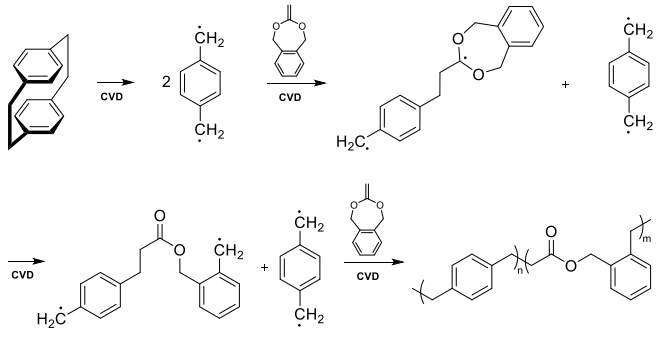
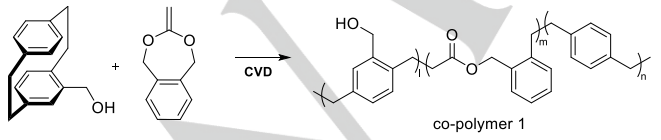


Scheme 1. Proposed mechanism of the CVD synthesis of backbone-degradable polymers. BMDO, a cyclic ketene acetal, was co-polymerized with radicals generated by the pyrolysis of [2.2]paracyclophanes. BMDO polymerized following a ring-opening radical polymerization mechanism, while undergoing a rearrangement into a polyester.

Using this approach, we co-polymerized [2.2]paracyclophane and BMDO at a molar ratio of 3:5. The resulting co-polymer (2) film was insoluble in common organic solvents, such as acetone, ethanol or isopropanol. The Fourier transform infrared spectroscopy (FTIR) spectrum of the polymer (supplementary information) shows a strong band at 1784 cm^{-1}, which is indicative of ester groups. The CVD-based co-polymer 2 degraded in 5 mM KOH/isopropanol solution at room temperature within 12 days, as confirmed by a successive loss of characteristic bands in the FTIR spectra and a continuous decrease in film thickness, as measured by ellipsometry (Figure S2c). In addition, the co-polymer film showed slow degradation in an aqueous bicarbonate buffer: At 37 °C, the film thickness of the polymer decreased by 11% after two months. From these results, we concluded that the ester bonds were indeed hydrolytically degradable, albeit the degradation proceeded relatively slowly. Apparently, the hydrophobicity of the polymer films prevented water penetration and slowed down the ester hydrolysis.

In order to accelerate the degradation in aqueous solution and incorporate functional groups for further surface modification, [2.2]paracyclophane was replaced with the more polar 4-hydroxymethyl-[2.2]paracyclophane. Co-polymerization with BMDO (Scheme 2) resulted in polymer films, which featured interfacial hydroxyl groups and showed increased hydrophilicity[22] compared to the earlier coatings.



Scheme 2. Synthesis of co-polymer 1 *via* CVD polymerization by feeding 1:15 molar ratio of 4-hydroxymethyl[2.2]paracyclophane (PCP-CH_2OH) and BMDO.

As described above, xylylene radicals generated by the pyrolysis of 4-hydroxymethyl[2.2]paracyclophane initiated the co-polymerization with BMDO to synthesize co-polymer 1. The resulting polymer films were characterized by a combination of surface-sensitive methods, including grazing angle Fourier-transformed infrared reflection absorption spectroscopy (IRRAS), and X-ray photoelectron spectroscopy (XPS). The FTIR spectrum of co-polymer 1 confirmed the existence of ester groups as indicated by a strong band at 1782 cm^{-1} (Figure 1a). Moreover, a broad band at 3446 cm^{-1} confirmed the presence of hydroxyl groups in the polymer film. XPS analysis further confirmed the preparation of co-polymer 1 (Table 1). The XPS survey spectrum reveals 16.4% oxygen and 83.6% carbon, which compares well to 15.7% oxygen and 84.3% carbon that can be calculated based on the structure of the monomers assuming a monomer feed ratio of 1:15 (PCP-CH_2OH: BMDO). The high-resolution C_{1s}-spectrum indicates the presence of carbon in different chemical states (59.5% C-C/C-H, 6.6% C-C=O, 9.7% C-O, 6.5% O-C=O), which is in good agreement with the theoretically calculated values.

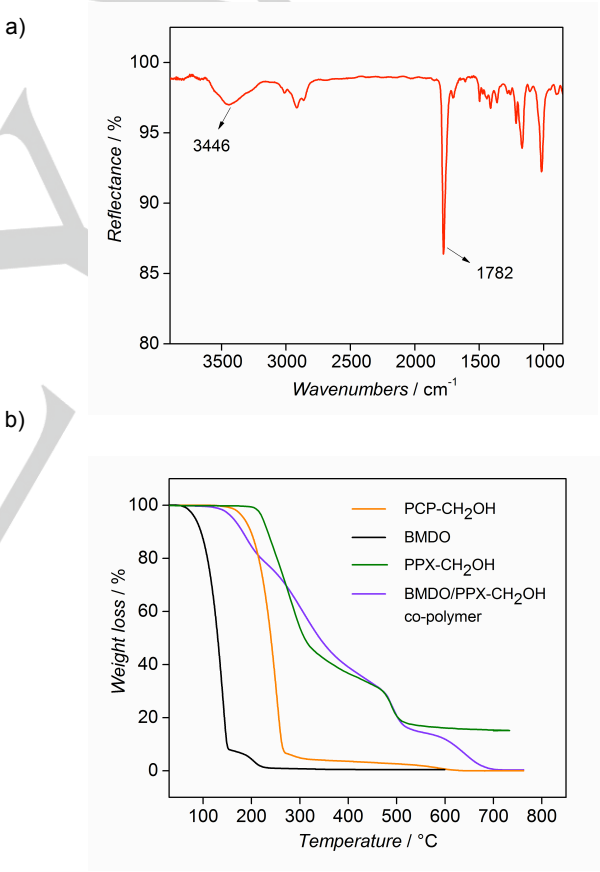


Figure 1. Polymer characterization: a) FTIR spectrum of co-polymer 1; b) TGA traces of the [2.2]paracyclophane and co-polymer 1 are compared to poly[(hydroxymethyl-*p*-xylylene)-*co*-(*p*-xylylene)] (PPX-CH_2OH).

In addition to the chemical analysis, thermogravimetric analysis (TGA) was performed for co-polymer 1 to confirm successful polymerization (Figure 1b). The CVD polymer films were compared to the respective monomers used for the CVD polymerization as well as a non-degradable

poly[(hydroxylmethyl-*p*-xylylene)-*co*-(*p*-xylylene)] (PPX-CH_2OH) film (Figure S5), which was also prepared by CVD polymerization. The results show that the different precursors and polymers have distinctly different TGA traces. The volatile BMDO monomer shows a two-step degradation with major weight loss in the temperature range from 67 °C to 151 °C and a second step of about 7% weight loss at a higher temperature range (190 °C to 220 °C), which is most likely due to a small portion of BMDO that underwent side reactions during storage. We extrapolated onset temperatures in nitrogen of 110 °C, 213 °C, 221 °C and 190 °C for BMDO, PCP-CH_2OH, PPX-CH_2OH and co-polymer 1, respectively. Co-polymer 1 shows a multi-step degradation, which is different from the degradation of the corresponding monomers. Its thermal stability is higher than the stability of the BMDO monomer, but lower than the thermal stability of PCP-CH_2OH. In contrast, PPX-CH_2OH follows a two-step degradation mechanism. The first infliction point occurs at 209 °C and may be due to loss of hydroxyl groups, whereas the second step occurs at 470 °C and can be explained by the thermal decomposition of the aromatic ring system. When heated up to 750 °C in nitrogen atmosphere, about 16% of carbon residues were still present, while no carbon residues were detected for co-polymer 1 under the same experimental conditions. The thermal stability of co-polymer 1 and PPX-CH_2OH is comparable, which confirms the potential for implementation of the hydrolytically degradable co-polymer 1 in various coating applications.

Table 1. XPS analysis results of co-polymer 1. Theoretical values were calculated from the chemical structure of the monomers of co-polymer 1 assuming a ratio of l:m:n = 1:15:1 (i.e., the precursor feed ratio).

	BE (eV)[a]	Theoretical (%)[b]	Experimental (%)[b]
C-C/C-H	285	61	59.5
C-C=O	285.7	7.6	6.6
C-O	286.7	8.1	9.7
O-C=O	289.3	7.6	6.5
π→π*	291.5	-	1.3
O	533	15.7	16.4

[a] Binding Energy. [b] Atomic percent.

After verification of the chemical composition of co-polymer 1, its degradation behavior was studied at 37 °C in an aqueous sodium carbonate buffer at a pH-value of 10.6 (Figure 2). From the FTIR spectra shown in Figure 2a, we confirmed decreasing intensities of vibrational bands characteristic of ester and hydroxyl groups at 1782 and 3446 cm^{-1}. In parallel, the thickness of the co-polymer 1 film (Figure 2b) continuously decreased over time, while the refractive index remained relatively constant around 1.5. Both, FTIR and ellipsometry data, are consistent with a surface erosion mechanism, where the ester groups of the topmost polymer chains are hydrolyzed first, which leads to the successive erosion of the following layers. The surface erosion process of co-polymer 1 appears to be controlled in an aqueous buffer and appears to be similar to the degradation of the polymer of non-functionalized [2.2]paracyclophane and BMDO (co-polymer 2) that occurred in the 5 mM KOH/isopropanol solution (supplementary information).

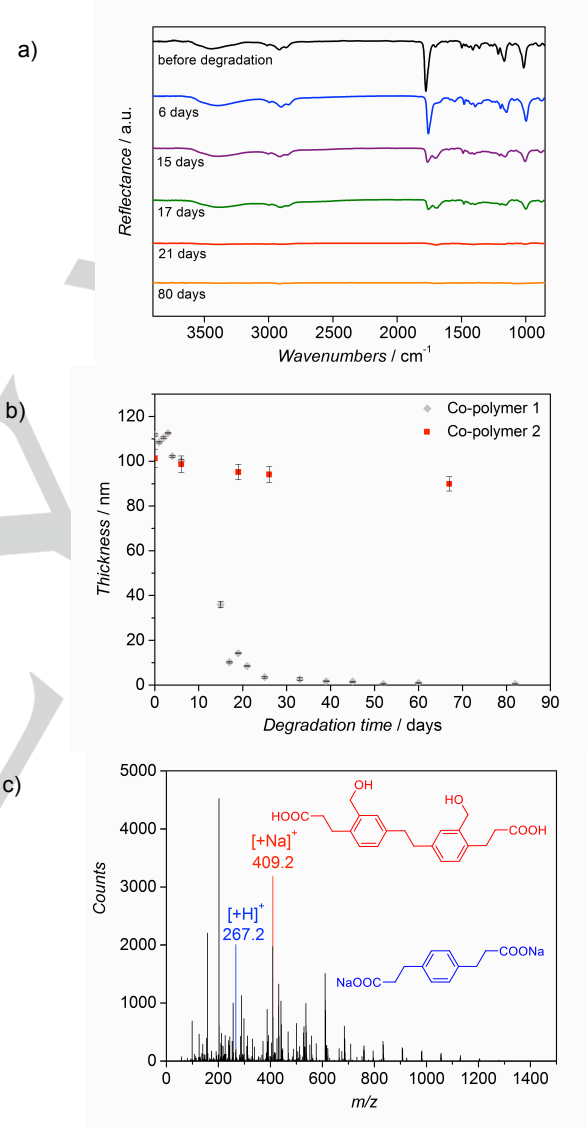


Figure 2. Polymer degradation: a) FTIR spectra of co-polymer 1 degrading over time. Co-polymer 1 was degraded in a sodium carbonate-sodium bicarbonate aqueous buffer solution with pH value of 10.6 at 37 °C; b) thicknesses of co-polymer 1 degrading over time measured by ellipsometry. Co-polymer 2 (co-polymer of [2.2]paracyclophane and BMDO) degrading in the same aqueous buffer solution (pH 10.6) is shown for the purpose of comparison; c) expanded ESI-mass spectra of the degradation products of co-polymer 1 after totally degradation (in the mass range m/z 200-500) with identified fragments.

We note that surface erosion may be more desirable than bulk erosion for some applications like drug delivery, because it can lead to more predictable release kinetics.[23-24] As shown in Figure 2a and 2b, co-polymer 1 is completely degraded after 80 days in the buffer, with 7.3% of the polymer film being degraded within the first 20 days. After degradation, we extracted the degradation products and analyzed them by positive electrospray ionization (ESI) mass spectrometry.[25] Among the degradation products were small molecule fragments with a mass below 1300 m/z. Some of the prominent fragments had mass-to-charge ratios (m/z) of 267.2 and 409.2 (Figure 2c). The fragmentation patterns support the assumption of ester bond cleavages further suggesting successive cleavage from both ends of the polymer chains. The fragment at m/z = 267.2 corresponds to the terminated carboxylate group and the fragmentation of the ion at m/z = 409.2 can be assigned to a product that is terminated by hydroxyl and carboxyl end groups. Based on this analysis, we concluded that the polymer formed by the CVD polymerization process has a random co-polymer structure. In the past, soluble PPX-films bearing alkyl substituents were characterized using GPC and NMR techniques.[26] The published results clearly confirmed the formation of linear CVD polymers. However, this approach requires the deposition of large polymer quantities, provided that the co-polymers are sufficently soluble in organic solvents suitable for NMR and GPC. A similar approach was not possible in this case. Instead, we base the preposition of linear co-polymers on the fragmentation patterns obtained by mass spectrometry. While preliminary in nature, these findings are consistent with the earlier findings by Greiner *et al*. for similar polymer films obtained by NMR and GPC.[26]

To assess the short-term cytotoxicity of these novel polymer coatings, we studied the cell viability of fibroblasts in direct contact with the polymers. Cell growth and confluency were examined under a phase contrast microscope (supplementary information). As a negative control, a poly(vinyl chloride) containing organ-tin compound (2 wt% dibutyltin maleate) was included and designed as Ot-PVC. The latter has been used as negative control to generate reproducible cytotoxic responses.[27] Non-coated TCPS (tissue culture polystyrene) was used as positive control. To quantify cell proliferation in response to exposure to the different surfaces, we employed a XTT assay, which is a commonly used colorimetric assay for detecting cell metabolic activities using cells in exponential growth phase.[28]

NIH3T3 fibroblasts were seeded on films comprised of either PPX-CH_2OH, co-polymer 1 or partially degraded co-polymer 1. These samples were compared to TCPS and Ot-PVC films. Figure 3 indicates increased spreading of actin filaments after cells were seeded on co-polymer 1 as well as partially degraded co-polymer 1, which are similar to those cultured on TCPS. No statistical differences were observed in the mitochondrial activity of cells seeded on the positive control or either of the CVD polymer coated samples, indicating that the CVD polymer surfaces were non-cytotoxic under these conditions. In contrast, the mitochondrial activity of cells seeded on the negative control was below the detectable limits of the assay. This is consistent with our imaging results, where cells seeded on co-polymer 1 did not exhibit signs of short-term toxicity, neither before nor after degradation.

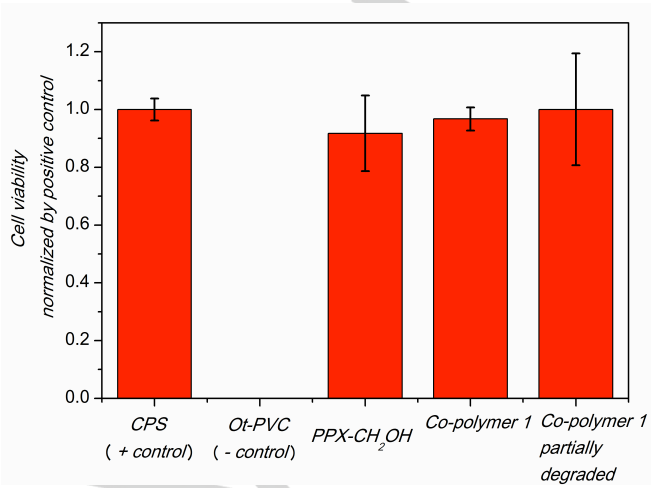


Figure 3. Cell viability test of co-polymer 1 before and after degradation. The results from XTT assay are presented as cell viability normalized by positive control, ± the standard deviation on different substrates. The experiments were carried out in triplicates.

To demonstrate surface immobilization onto simultaneously functionalized and degradable CVD coatings, we conducted co-polymerization of alkyne-functionalized 4-ethynyl[2.2]para-cyclophane with BMDO resulting in the novel co-polymer 3 (Figure 4a). Experimentally, the CVD co-polymerization followed the protocol previously described for the synthesis of co-polymer 1. The FTIR spectrum of co-polymer 3 (Figure 4b) reveals characteristic bands of the ester groups (1780 cm^{-1}) as well as the terminal alkyne groups at 3300 cm^{-1} and 2100 cm^{-1}, respectively. The FTIR data are further confirmed by the XPS results (Table S1).

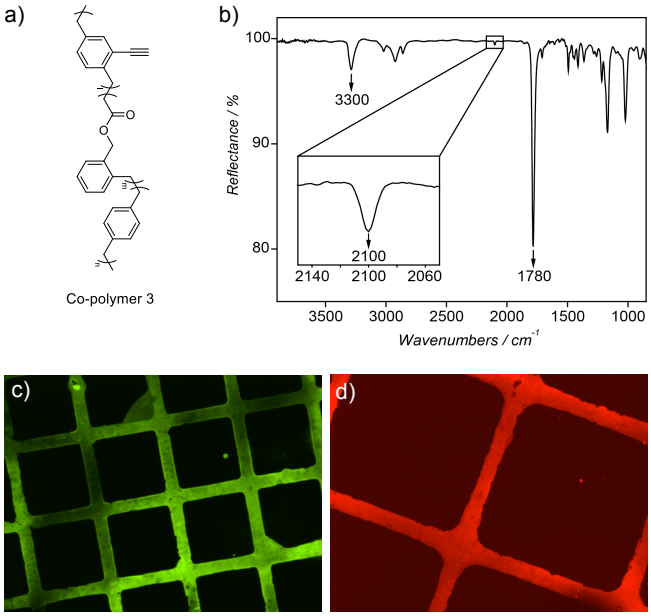


Figure 4. CVD co-polymerization of BMDO and 4-ethynyl[2.2]paracyclophane: a) chemical structure of the biodegradable co-polymer 3 (polymer of 4-ethynyl[2.2]paracyclophane and BMDO with the precursor feed ratio 1:5); b) FTIR spectrum of co-polymer 3; c) fluorescence micrograph after microcontact printing (μCP) Alexa Fluor 488 azide on the co-polymer 3 surface; d) fluorescence micrograph after μCP biotin-PEG_3-azide and streptavidin-Cy3 immobilization.

The chemical reactivity of the alkyne-functionalized surfaces was confirmed by copper-catalyzed azide-alkyne cycloaddition (CuAAC), a well-known "click" reaction.[29] Specifically, the surface of co-polymer 3 was patterned via spatially controlled click reaction using microcontact printing (μCP). Microcontact printing is a commonly used method to generate micron-scale patterns and has been used in the past for spatially controlled immobilization of biomolecules onto functionalized poly(*p*-xylylene)s.[13]

Immobilization of Alexa Fluor@ 488 azide (Figure 4c) was achieved using a microstructured PDMS stamp that was inked with a solution of CuSO4 and brought into contact with the polymer substrate. Next, the covalent binding of a biotin-PEG3-azide followed by streptavidin-Cy3 was used for visualization of the selective modification (Figure 4d). Figures 4c and 4d verify the specific reactivity towards the alkyne groups presented on the copolymer surface

In summary, we have demonstrated the successful synthesis of a novel class of backbone-degradable CVD polymer thin films, which combine the attractive characteristics of both, degradability and chemical functionality for subsequent surface modification. The synthesis was achieved by polymerization of a cyclic ketene acetal, BMDO, with functionalized [2.2]paracyclophanes via CVD polymerization. The co-polymers were hydrolytically degraded and show no obvious short-term cytotoxicity in a XTT assay. In addition, both, the functionality and the precursor feed ratios, can be controlled in order to create different combinations of interfacial and bulk properties. This new class of degradable functional thin films has the potential to serve as a widely applicable surface functionalization and coating platform for a broad spectrum of technologies ranging from the life sciences, and medicine to food packaging applications.

Experimental Section

CVD precursors: The non-functionalized [2.2]paracyclophane (PCP-N) was purchased from *Parylene Coatings Services Inc.*. 4-Hydroxymethyl[2.2]paracyclophane (PCP-CH_2OH) and 4-ethynyl[2.2]paracyclophane (PCP-alkyne) were synthesized as reported previously.[30-31] 5,6-Benzo-2-methylene-1,3-dioxepane (BMDO) was synthesized according to literature-known procedures with slight modifications.[18-20] The detailed synthesis is described in the supplementary information section. **CVD polymerization:** The degradable polymers were synthesized by feeding a selected [2.2]paracyclophane derivative together with BMDO into the CVD system. The feed ratio of the precursors is variable. For the synthesis of co-polymer 1, the molar ratio of the two precursors PCP-CH_2OH and BMDO was 1:15. For co-polymer 2, the molar ratio of PCP and BMDO was 3:5. For co-polymer 3, the molar ratio of PCP-alkyne and BMDO was 1:5. The precursors sublimated or evaporated under 0.07 Torr at around 100 °C and were then transferred to the pyrolysis zone (530 °C) using a stream of argon carrier gas (20 sccm). Radicals generated from the pyrolysis of [2.2]paracyclophanes were further transferred into the deposition chamber together with the vaporized BMDO. The radicals and BMDO adsorbed and polymerized on the substrates placed on a metal stage set at 15 °C. The CVD deposition rate was kept at 0.1 to 0.2 Å/s and was constantly monitored by a quartz crystal microbalance (QCM). **Polymer Characterization:** Co-polymer 1 was characterized by FTIR, XPS and TGA. All FTIR data reported in this study were generated using a Nicolet 6700 spectrometer with a MCT-A detector and a smart specular apertured grazing angle (Smart SAGA) accessory with an 80° fixed angle of incidence. XPS was performed on a Kratos Axis Ultra XPS equipped with a monochromatic Al Kα X-ray source. Passing energy applied was 160 eV for survey scans and 20 eV for high-resolution analysis. All spectra were calibrated in reference to the non-functionalized aliphatic carbon with peak position fixed at 285.0 eV. TGA experiments were performed on a TA Instruments Discovery TGA with a heating rate of 10 °C/min in the range from 20 °C to 750 °C in nitrogen atmosphere with a purge rate of 25 mL/min. **Polymer Degradation:** Gold (100 nm by e-beam evaporation, with 10 nm Ti as adhesion layer) coated polished silicon surfaces were used as substrates to facilitate Fourier transform infrared spectroscopy (FTIR) and ellipsometry measurements, which were used to monitor the film degradation process. Samples coated with co-polymer 1 were incubated in an aqueous solution with 0.1 M sodium bicarbonate and 0.1 M sodium carbonate (v/v=9:1, Na_2CO_3/$NaHCO_3$) at 37 °C. The pH value of this degradation solution was 10.6 at 37 °C. At different time intervals, the samples were taken out of the degradation solution, washed thoroughly with deionized-water and air-dried. Then the samples were measured by FTIR and ellipsometry (Accurion, Nanofilm EP^3-SE, Germany) to monitor their change in chemical composition and thickness. Ellipsometric parameters were fitted using a *Cauchy* model. After full degradation of co-polymer 1 coatings, the degradation solution was extracted with chloroform and analyzed by Electrospray Ionization–Mass Spectrometry (ESI-MS) to analyze the final degradation products. **Cell viability tests:** Tissue culture polystyrene (TCPS) coverslips (Thermo Scientific Nunc Thermanox Coverslips) were coated with PPX-CH_2OH or co-polymer 1.

Some of the samples coated with co-polymer 1 were degraded for 5 days before the cell viability test. TCPS itself served as a positive control and organ-tin (dibutyltin maleate, 2 wt%) stabilized PVC (Ot-PVC) with high cytotoxicity was used as a negative control. NIH/3T3 cells were cultured at 37˚C, 5% CO_2 in DMEM with 10% FBS. Cells were then passaged after reaching 80% confluence and seeded onto the non-coated TCPS, the CVD coated TCPS and the Ot-PVC at a density of $1x10^4$ cells/cm^2. The cells were then cultured at 37˚C under 5% CO_2 for 3 days. After 3 days in culture, the medium was removed and replaced with fresh medium. Cytotoxicity was then determined using an XTT cell proliferation assay kit (ATCC, Manessa VA). Activated XTT solution was added to the medium and incubated at 37˚C under 5% CO_2 for 2 hours. Next, the absorbance of the medium was measured using a microplate reader (BioTek Synergy 2, Winooski VT) at two wavelengths, 475 nm and 660 nm. Cell viability was determined by normalizing the measured mitochondrial activity of the NIH/3T3 cells expanded on CVD coated TCPS with cells expanded on non-coated TCPS. **Surface reactivity test:** In order to test the surface reactivity of co-polymer 3 (co-polymer of PCP-alkyne and BMDO with a molar feed ratio of 1:5), copper catalyzed alkyne-azide click chemistry[31-32] was applied on the surface using micro-contact printing. The fabrication of the mold and polydimethylsiloxane (PDMS) stamps for micro-contact printing is described elsewhere.[33-34] PDMS stamps were first oxidized by UV ozone treatment for 30 minutes in order to facilitate the wetting process. One type of "ink" applied was an aqueous solution consisting of 5 µg/ml Alexa Fluor 488 azide (Life Technologies), 20 mg/ml sodium ascorbate and 1 mM copper sulfate pentahydrate. The other type of "ink" applied was an aqueous solution consisting of 0.2 mg/ml biotin-PEG_3-azide (Sigma-Aldrich), 20 mg/ml sodium ascorbate and 1 mM copper sulfate pentahydrate. The printing time was 2 hours for both inks and the printed samples were thoroughly washed with deionized water afterwards. Since the second ink did not contain a fluorescent dye, samples with biotin immobilized on the surface were incubated in 5 µg/ml Streptavidin-Cy3 (Sigma-Aldrich) PBS solution with 1 mg/ml bovine serum albumin (BSA) for half an hour in order to visualize the pattern. Biotin and streptavidin are biomolecules which are often used as a model in biomedical research due to their high binding affinity to each other.[35] BSA was added to stabilize the protein in the solution and prevent nonspecific binding of the protein on the coating surface. The surface was thoroughly rinsed with BSA/PBS solution, PBS solution and deionized water before fluorescence imaging.

Acknowledgements

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X.D., C.F. and J.L. conceived the initial idea. C.F. and D.K. synthesized the CVD precursors (BMDO and the [2.2]para-cyclophane derivatives). X.D. conducted the initial CVD polymerization experiments, characterized the thin films, carried out the degradation experiments and analyzed the results. L.S. performed the cell viability tests and analyzed the results. F.X. and K.C. carried out the CVD polymerization experiments, characterized the thin films, carried out the degradation experiments and analyzed the results with X.D. Finally, D.K., X.D., K.C. and J.L. wrote the manuscript with contributions from all authors.

Keywords: Free radical ring opening polymerization • cyclic ketene acetal • hydrolytic degradation • hydrolytically degradable functional polymers • CVD polymerization

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Supporting Information

Backbone-Degradable Polymers *via* Chemical Vapor Deposition

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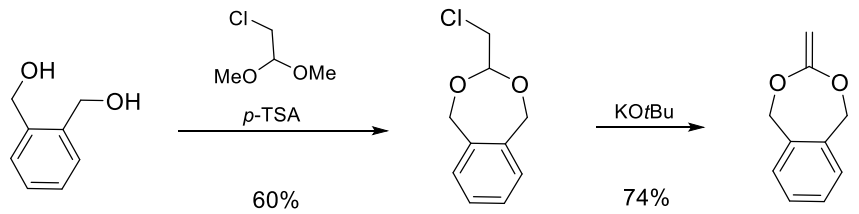
Synthesis of BMDO



Scheme S1. Synthesis of 5,6-benzo-2-methylene-1,3-dioxepane (BMDO). The product was synthesized via a slightly modified literature-known procedure.[1-3]

Synthesis of 2-(chloromethyl)-5,6-benzo-1,3-dioxepane

1,2-Benzendimethanol (16.3 g, 118 mmol), chloracetaldehyde dimethyl acetal (14.0 mL, 122 mmol) and *p*-toluenesulfonic acid (105 mg, 0.60 mmol) were dissolved in diglyme (33 mL) and the flask was equipped with a 3-way 75° bend distillation head adapter and a flask to collect the generated methanol. The mixture was heated to 150 °C and stirred for 24 hours until no more methanol was collected. After cooling to room temperature the reaction solution was poured into hexane (200 mL). The precipitated product was isolated. After washing with hexane (3 x 80 mL) the product was obtained as a white solid (14.2 g, 60%). – **^{1}H-NMR** (500 MHz, $CDCl_3$): 7.29–7.20 (m, 4H, aromatic), 5.12 (t, J = 5.1 Hz, 1H, OC*H*), 4.98 (d, J = 14.5 Hz, 2H, OCH_2), 4.95 (d, J = 14.5 Hz, 2H, OCH_2), 3.63 (d, J = 5.1 Hz, 2H, CH_2Cl) ppm. – **^{13}C-NMR** (125 MHz, $CDCl_3$): 138.5, 127.8, 127.5, 106.2, 72.0, 43.9 ppm. Spectroscopic data is in agreement with the literature.[1-3]

Synthesis of 5,6-benzo-2-methylene-1, 3-dioxepane

Under argon, 2-(Chloromethyl)-5,6-benzo-1,3-dioxepane (11.2 g, 56.1 mmol) and potassium *t*-butoxide (7.74 g, 69.0 mmol) were dissolved in tetrahydrofuran (125 mL) and the mixture was heated to 50 °C. After 72 hours the suspension was cooled to room temperature and the solvent was removed under reduced pressure. Next, diethyl ether (350 mL) was added and the solid was filtered. After removal of the solvent, the crude

product was purified by vacuum distillation (0.001 bar, 62 °C) to yield the product as a colorless liquid that crystallized upon standing at room temperature (6.76 g, 74%). – **^{1}H-NMR** (500 MHz, $CDCl_3$): 7.29–7.26 (m, 2H, aromatic), 7.13–7.10 (m, 2H, aromatic), 5.09 (s, 4H, OCH_2), 3.75 (s, 2H, CH_2) ppm. – **^{13}C-NMR** (125 MHz, $CDCl_3$): 164.2, 135.8, 127.4, 126.2, 72.1, 69.5 ppm. The spectroscopic data are in agreement with the literature.[1-3]

Additional information on co-polymer 1

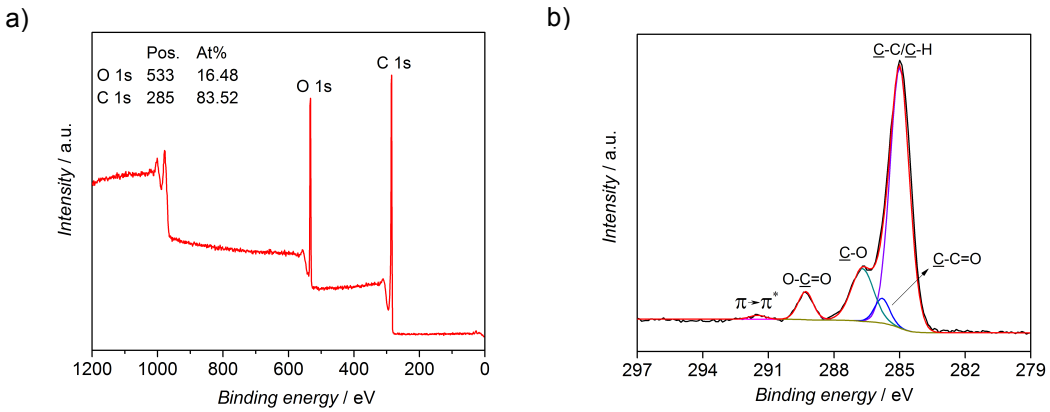
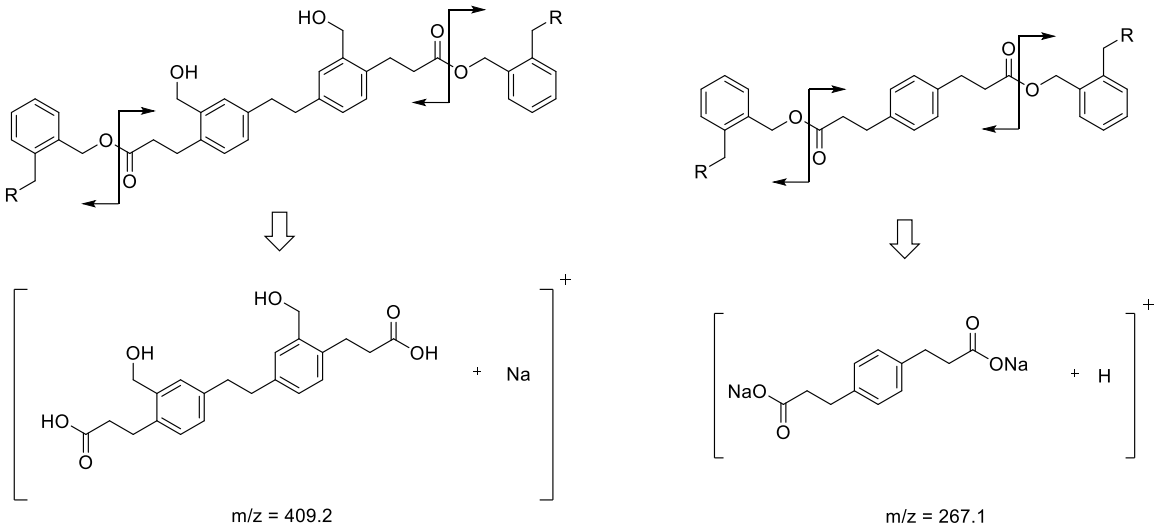


Figure S1. (a) XPS survey spectrum of co-polymer 1; (b) high resolution XPS C 1s spectrum of co-polymer 1 (co-polymer of 4-hydroxymethyl-[2.2]paracyclophane and BMDO).



Scheme S2. Possible fragmentation patterns of co-polymer 1 after degradation. The carboxyl terminated products could be detected by ESI-MS analysis.

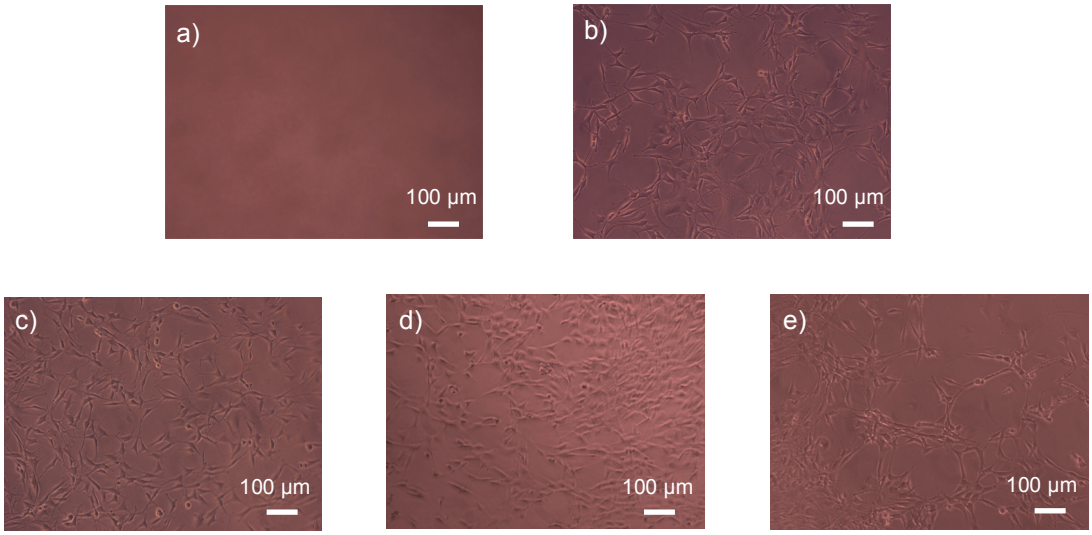
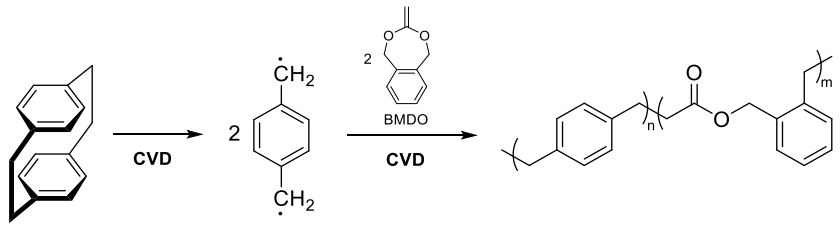


Figure S2. Microscopy images of NIH3T3 fibroblasts grown on different surfaces for the XTT cell viability assay: (a) poly(vinyl chloride) (PVC) surface (negative control); (b) TCPS (positive control); (c) PPX-CH_2OH; (d) co-polymer 1; (e) co-polymer 1 partially degraded. NIH3T3s show different spreading responses with respect to the different surfaces.

Additional information on co-polymer 2



Scheme S3. Synthesis of co-polymer 2 *via* co-polymerization of [2.2]paracyclophane and BMDO (feeding molar ratio 3:5).

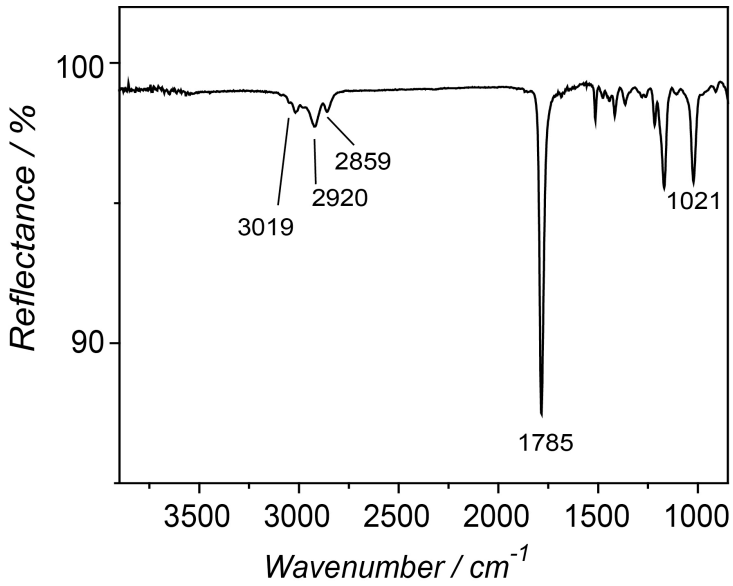


Figure S3. FT-IR spectrum of co-polymer 2 film. The film has been stable in carbonate buffer for at least two weeks and no reduction of its ellipsometric thickness has been observed during that period.

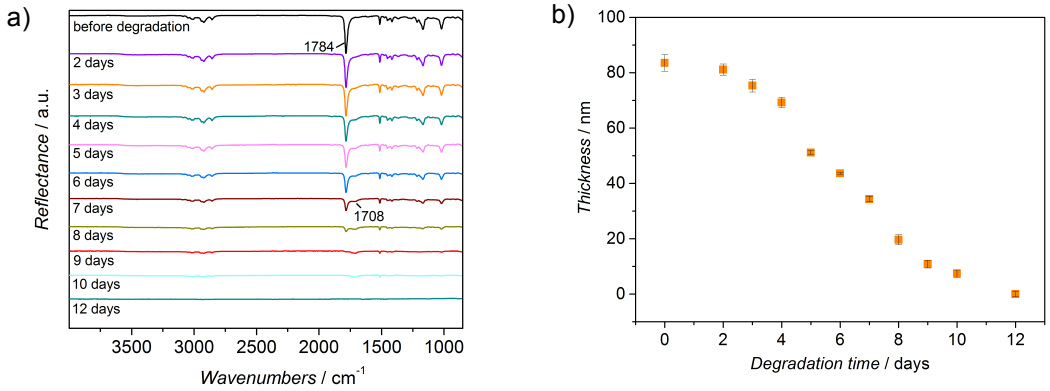


Figure S4. (a) FT-IR spectra of co-polymer 2 degrading in 5 mM KOH/isopropanol solution; (b) changes in the layer thickness of co-polymer 2 degrading in 5 mM KOH/isopropanol solution measured by ellipsometry.

Additional information on PPX-CH_2OH

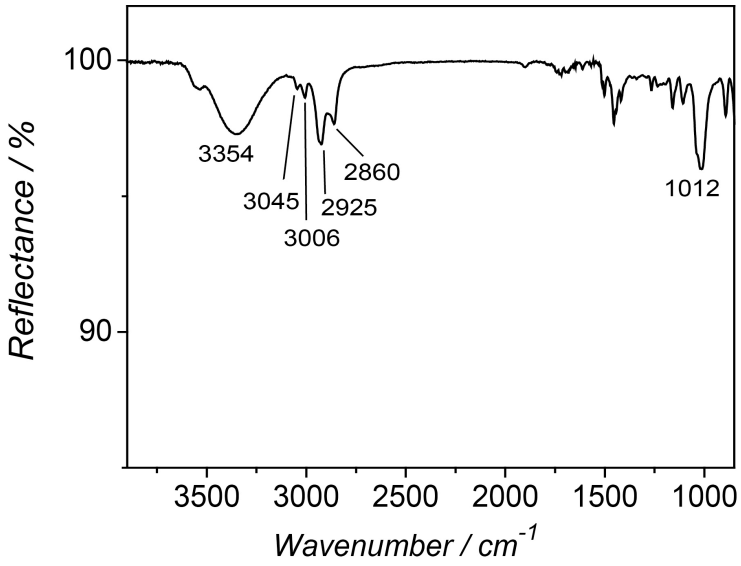


Figure S5. FT-IR spectrum of PPX-CH2OH film. The thickness of the polymer film is 88 nm, as measured by ellipsometry.

Additional information on co-polymer 3

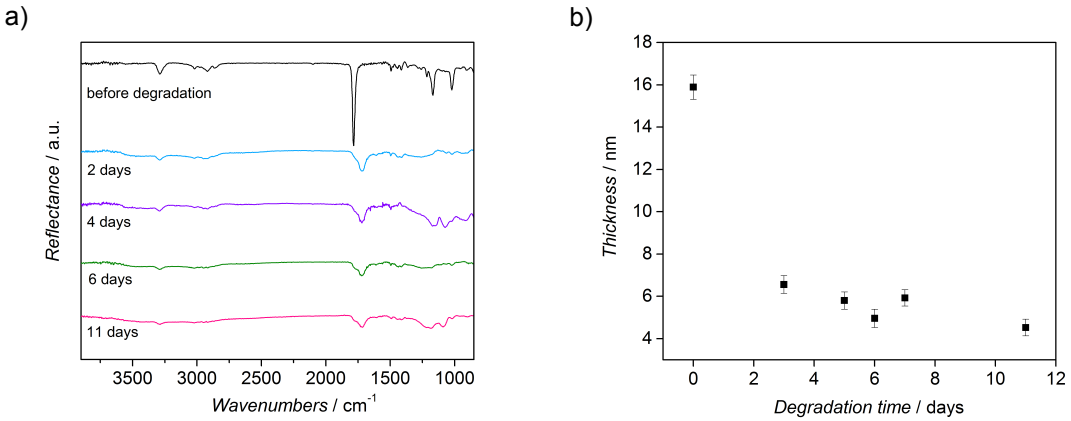


Figure S6. (a) FTIR spectra of co-polymer 3 degrading over time; (b) changes in the layer thickness of co-polymer 3 degrading in 5 mM KOH/isopropanol solution measured by ellipsometry.

Table S1. XPS analysis results of co-polymer 2 and 3.

	B.E. (eV)[a]	**Co-polymer 2** experimental (%)[b]	**Co-polymer 3** experimental (%)[b]
C-C/H	285±0.1	68.1	69.1
C-C=O	285.7±0.1	6.8	8.3
C-O	286.8±0.1	7.6	8.7
O-C=O	289.3±0.1	4.2	4.9
π→π*	291.5±0.1	1.3	1.0
O	533±0.1	12.0	8.0

[a] Binding Energy; [b] Atomic percent.

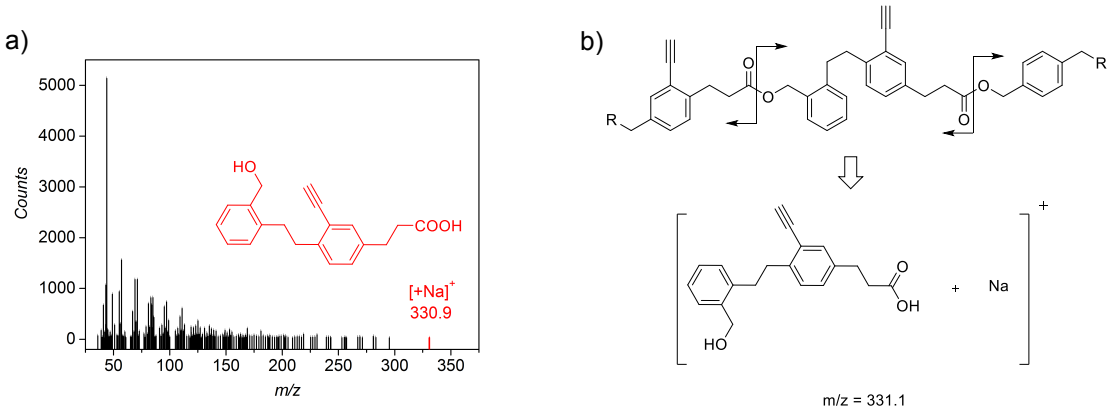


Figure S7. (a) Expanded ESI-mass spectrum of degradation products of co-polymer 3; (b) possible fragmentation pattern of co-polymer 3 after degradation.

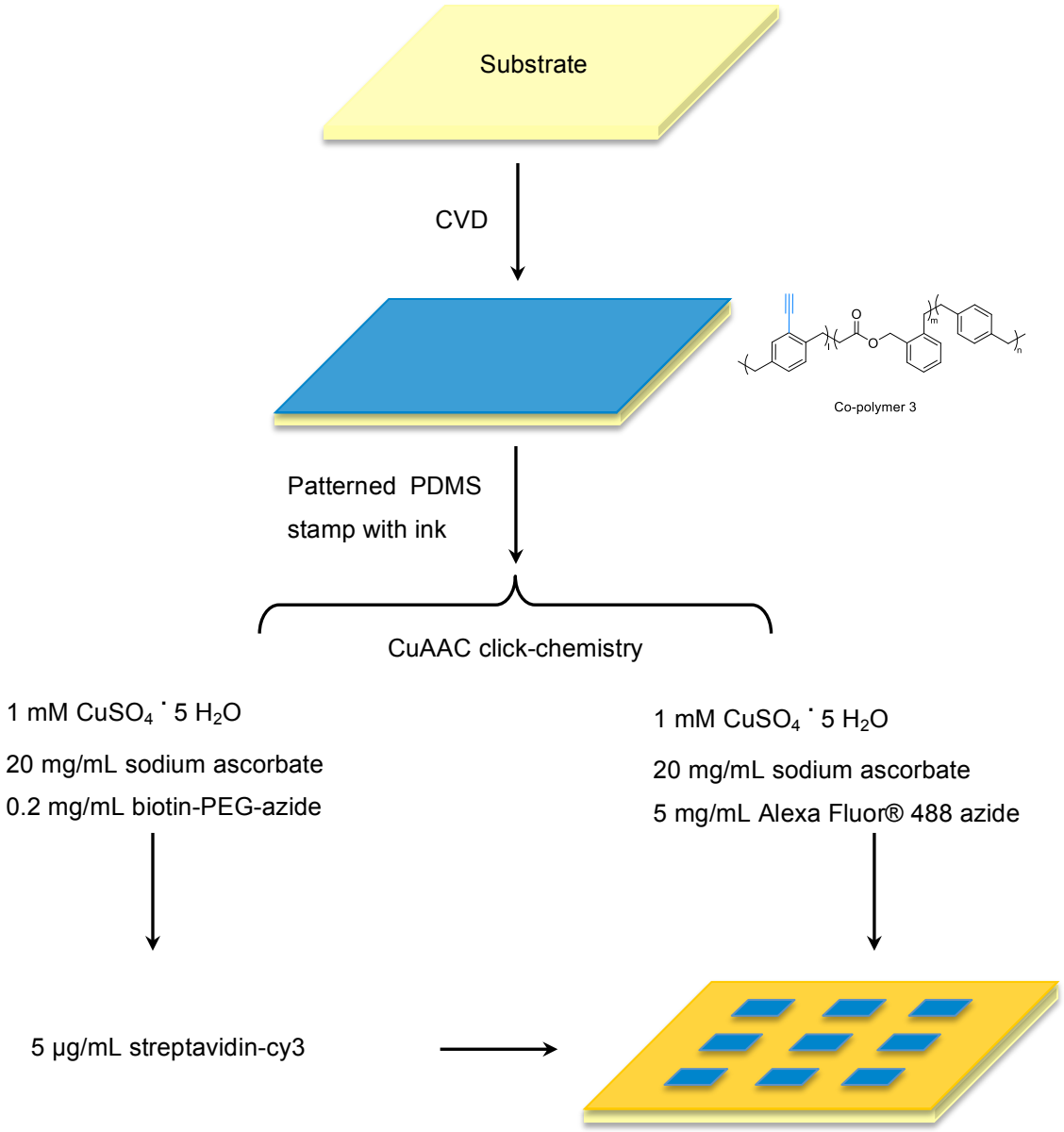


Figure S8. Schematic illustration showing the click-chemistry procedure used to demonstrate the chemical activity of co-polymer 3.

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[3] G. G. d'Ayala, M. Malinconico, P. Laurienzo, A. Tardy, Y. Guillaneuf, M. Lansalot, F. D'Agosto, B. Charleux, *J. Polym. Sci., Part A: Polym. Chem.* **2014**, *52*, 104-111.