

n-Alkyl Fatty Acid-Modified Microgels: Ion Permeation as a Function of Chain Length

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Saturated *n*-alkyl fatty acid chlorides (CH₃(CH₂)_{*n*}COCl where *n* = 0, 2, 4, 6, 8, 10, 12, and 14) were covalently attached to pH-sensitive hydrogel objects (μ gels) within microfluidic systems using an in situ process. Staining with a lipophilic dye indicated that the resulting fatty acid layer was confined to the periphery of the μ gel. The barrier properties of these fatty acid coatings were investigated by determining the half-life of μ gel expansion after exposure to a buffer solution that triggers swelling of unmodified μ gels. For *n* = 0, the half-life values were similar to those for unmodified μ gels, indicating that no significant ion gradient was established. Considerably longer half-lives were observed for μ gels modified with *n*-alkyl fatty acid layers with *n* \geq 2 carbons, as these μ gels significantly retarded ion penetration. However, the half-lives of μ gel expansion did not increase as the fatty acid chain lengthened, suggesting that the utilization of a hydrogel substrate involves additional factors (e.g. pinhole defects) that influence the permeability of the fatty acid coatings to a greater degree than the alkyl chain length.

Introduction

Self-assembled monolayers (SAMs) are extensively utilized to modulate the chemical and physical properties of surfaces.^{1,2} Research on SAMs mainly focuses on ordered organic molecules covalently or noncovalently organized on solid surfaces, including thiols on gold, silanes on glass or silicon, and phospholipid bilayers on inorganic substrates.^{2–11} The creation of SAMs on substrates whose surfaces are dynamic and poorly defined, such as polymeric materials, has not been as thoroughly studied. Whitesides and co-workers first reported the formation of alkylsiloxane monolayers on polyethylene and poly(dimethylsiloxane) surfaces, which could be further derivatized with a variety of terminal functionalities.^{12–15} Characterization with contact angle measurements, X-ray photoelectron spectroscopy, and infrared spectroscopy indicated the monolayer existed in a liquidlike state with wetting behavior comparable to that of analogous SAMs formed on silicon. The production of more elaborate SAMs that were functionalized with photopatternable end groups

was reported by Bohme and co-workers.^{16,17} Bolaamphiphiles, or hydrophobic molecules substituted with two polar headgroups, were used to modify poly(acrylonitrile) or poly(allylamine hydrochloride) films. Exposure of the azide moieties located at the monolayer surface to UV radiation resulted in the formation of nitrene intermediates that could be employed for further functionalization. Recently, Ratner and co-workers developed a method to deposit SAMs on hydrogels to improve their biocompatibility.¹⁸ Dodecyl isocyanate was used to modify the surface of poly(2-hydroxyethyl methacrylate), producing a crystalline multilayer of alkyl urethanes.

The surface properties that result from the deposition of SAMs on polymeric materials are not solely governed by the chemical composition of the molecules assembled at the surface, as the behavior of self-assembled amphiphiles on hydrogel substrates can vary from that of those supported by solid substrates.^{19,20} As a key example, self-assembled phospholipid bilayers partially tethered to the surface of hydrogels can provide an environment that better mimics a cell membrane for transmembrane protein incorporation than bilayers assembled on solid surfaces.^{19–23} In addition to serving as an improved biomimetic model of a cell membrane, the lipid layer forms a thin semipermeable barrier that is able to maintain a chemical gradient.²⁴ These properties have inspired the

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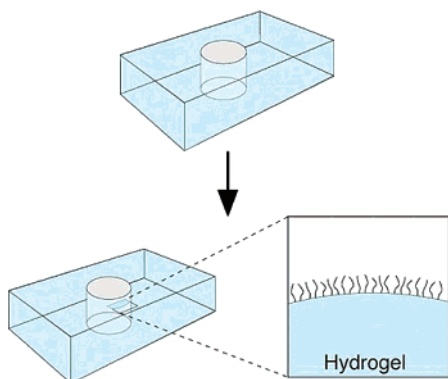
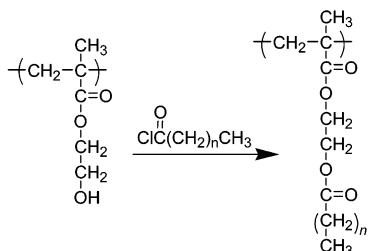


Figure 1. Esterification of the μ gel with various fatty acid chlorides creates a covalently linked lipophilic layer.

Scheme 1



preparation of novel hybrids that combine lipids and hydrogels for sensory or drug delivery applications.^{25–30}

Previously, we described an *in situ* method to covalently attach a coating of fatty acids to the periphery of pH-sensitive hydrogel objects (μ gels) within microchannels (Figure 1 and Scheme 1).^{27,31} The influx of ions into the μ gel is inhibited by the fatty acid coating, thereby establishing an ion gradient that allows the μ gel to remain contracted when bathed in a buffer solution that otherwise triggers expansion of unmodified samples. In this study, we report the influence of the fatty acid chain length on the ion gradient stability, which is examined by measuring the half-life for μ gel expansion of various *n*-alkyl fatty acid-modified samples exposed to a buffer solution that elicits swelling of the hydrogel matrix. Because this behavior seems to be defect-dominated and therefore subject to large variations, we have examined large numbers of samples for each chain length. The experimental results are evaluated to assess whether this method for fatty acid assembly at the gel–liquid interface of 3-dimensional hydrogel objects produces permeability behavior that is comparable to that of more traditional SAMs.

Experimental Section

Materials. Acrylic acid (AA, Fisher Scientific) and 2-hydroxyethyl methacrylate (HEMA, Aldrich) were each vacuum distilled in the presence of the polymerization inhibitor 4-methoxyphenol prior to use. 2,2-Dimethoxy-2-phenylacetophenone (DMPA, Aldrich), phenolphthalein (Aldrich), palmitoyl chloride (Aldrich),

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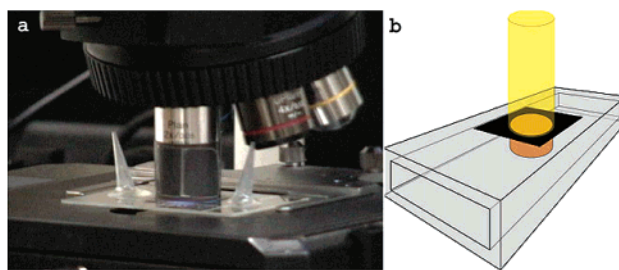


Figure 2. Photomask positioned on the microchannel containing the liquid prepolymer cocktail. Exposure of the unmasked region to UV light intensified by a microscope objective (a) produces a hydrogel pillar. Sketch of the photopolymerization process (b). Fatty acid modification takes place directly in the microchannel following polymerization.

lauroyl chloride (Aldrich), myristoyl chloride (Aldrich), decanoyl chloride (Aldrich), octanoyl chloride (Aldrich), hexanoyl chloride (Aldrich), butyryl chloride (Aldrich), acetyl chloride, (Acros), 4-(dimethylamino)pyridine (DMAP, Aldrich), benzene (Fisher), triethylamine (NEt₃, Fisher), phosphate dibasic (analytical reagent grade, Fisher Scientific), 1,1'-dioctadecyl-3,3,3',3'-tetramethylindolodicarbocyanine perchlorate (DiD, Molecular Probes), ethylene glycol dimethacrylate (EGDMA, Aldrich), and sodium hydroxide (Aldrich) were all used as received without purification.

Instrumentation. Photopolymerization was performed with an Olympus Epifluorescent microscope (BX-60) equipped with a high-pressure Hg lamp and a UV filter cube with a 360–370 nm band-pass (U-MNUA, type BP360-370). Photomasks of circles (400 μ m diameter) were printed on transparency film using a high-resolution printer (5080 dpi, Linotype Herkules Imagesetter, Heidelberg, Germany). Surface modifications were performed with a Harvard Apparatus PHD 2000 remote control with 6/10 Multi-Rack programmable syringe pump, which allowed the modification of up to six μ gels at a time. A Corning 307 pH meter was used to determine the pH of the buffer solutions. Expansion of the modified μ gels was monitored with a Zeiss Axioskop 50 microscope equipped with a Zeiss ZVS-47N main power supply, a JVC HR-S4900U video cassette recorder, and a Sony TRINITRON PVM-1343MD video monitor. Imaging of fluorescent dyes was performed with a Leica TCS SP2 laser scanning confocal microscope (LSCM) using the 20 \times objective and a near-IR laser (Spectral Physics, 780 nm) for excitation.

In Situ Polymerization of μ gels. pH-sensitive μ gels were photopolymerized within glass microchannels by our previously reported method.³² Briefly, a glass microchannel was filled with a liquid prepolymer cocktail consisting of HEMA, AA (4:1 vol ratio), EGDMA (1 vol %), DMPA (3 wt %), and phenolphthalein (1 wt %) and placed on the stage of the microscope. A photomask was positioned in the desired location on top of the channel, and irradiation of the unmasked region with UV light intensified by the 2 \times lens for 2 min produced a pH-sensitive μ gel 180 μ m tall by 400 μ m in diameter constrained at the top and bottom by the glass channel (Figure 2). After polymerization, the channel was flushed with methanol and acetone and the inlet was attached to a N₂ line via silicone tubing (1.58 mm i.d., 2.41 mm o.d., HelixMark) to dry overnight.

Modification of μ gels with *n*-Alkyl Fatty Acids. Saturated *n*-alkyl fatty acid chlorides (CH₃(CH₂)_nCOCl where *n* = 0, 2, 4, 6, 8, 10, 12, and 14) were used to esterify the hydroxyl functionalities at the surface of pH-sensitive μ gels using the previously described procedure.²⁷ Briefly, to prepare each μ gel, a 50 mL syringe was charged with a vacuum filtered (medium frit) solution of 0.1 M selected fatty acid chloride, 0.1 M NEt₃, and 0.01 M DMAP in benzene. The syringe was fitted with a 16-gauge needle, and silicone tubing was used to connect the inlet of a channel that contained a μ gel to the needle and the outlet of the channel to a waste container. Using a syringe pump, the solution was flowed through the channel at a rate of 5 mL/h until the syringe was half empty (ca. 4.5 h). The channel was flushed with CH₂Cl₂, the tubing and needles were replaced, and

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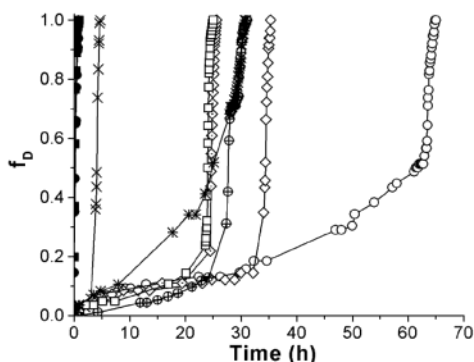


Figure 3. Fractional change in diameter against time. Unmodified pH-sensitive μ gels (■) and those modified with acetyl chloride (●) expand with a diameter change that followed a first-order exponential decay after exposure to pH 12 buffer solution. Modification with longer fatty acids (\times , \circ , \diamond , \oplus , dot in a diamond, \square , and $*$ are $n = 2, 4, 6, 8, 10, 12$, and 14 , respectively) delayed the expansion process and gave behavior that significantly deviated from a first-order exponential decay.

the remaining solution was flowed through the channel in the opposite direction than that previously employed. For modification at extended time intervals, this procedure was repeated with fresh solution until the desired duration was reached. After modification, the channel was flushed with CH_2Cl_2 to remove unreacted reagents and placed on a N_2 line to dry.

Half-life of Expansion Value Measurement. To test the properties of the n -alkyl fatty acid modified hydrogels, pH 12 phosphate buffer was flowed into the channel, and the relative μ gel diameter was measured at timed intervals on the video monitor. These data were plotted as f_b versus time, where f_b is the fractional change in the μ gel diameter. $f_b = (d - d_i)/(d_f - d_i)$; d is the diameter at the timed interval, d_i is the diameter in neutral water, and d_f is the final diameter of the fully expanded μ gel. In the event that the μ gel broke during expansion, d_f was estimated to be the same as that determined in similar samples, which was fairly constant. The half-life for expansion, designated as the time interval for each μ gel to reach an f_b of $\ln 2$, was determined from the resulting plot. To achieve statistically meaningful results, a total of 50 samples were examined for each n -alkyl fatty acid chloride (10 samples when the longer reaction time was employed), and the mean half-life and error bar at the 95% confidence level were determined for each set of 50 runs with standard statistical analysis methods.

Addition of Lipophilic Dye to Modified μ gels. A solution of 5 mg/mL of 1,1'-dioctadecyl-3,3',3'-tetramethylindolylidocarbocyanine perchlorate (DiI) in methylene chloride was introduced to the channel containing the modified μ gel. After 30 min at room temperature the channel was rinsed with 5 mL of acetone and 5 mL of water. Two samples were stained for subsequent imaging with LSCM for each n -alkyl fatty acid chloride employed.

Results and Discussion

To investigate the barrier properties of the resulting layers, the μ gels modified with various fatty acids chlorides ($\text{CH}_3(\text{CH}_2)_n\text{COCl}$ where $n = 0, 2, 4, 6, 8, 10, 12$, and 14) were bathed in a buffer solution that initiates immediate expansion in unmodified μ gels. Figure 3 shows representative curves of the fractional change in diameter (f_b) as a function of time following the introduction of buffer. An unmodified (control) μ gel is shown for comparison. For the control (■), expansion began uniformly on the surface and symmetrically progressed to the center (Figure 4a–c), accompanied by a change in color from colorless to pink resulting from the phenolphthalein indicator. Expansion was complete in under an hour, and the change in diameter as a function of time followed a first-order exponential decay. Similar behavior was demonstrated by μ gels modified with the shortest fatty acid chloride ($n = 0$, acetyl chloride, Figure 3, ●). Expansion also began

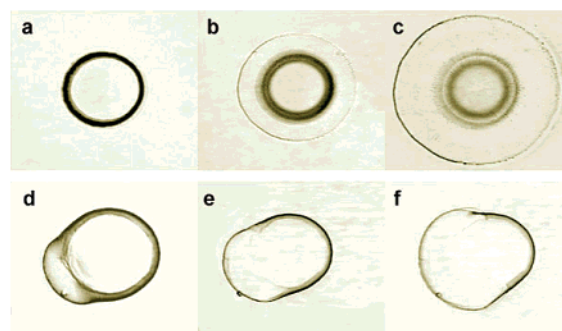
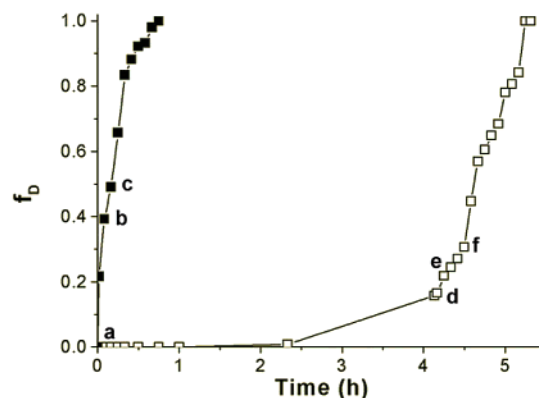


Figure 4. (a–c) Expansion on the perimeter of unmodified μ gels is uniform and follows an exponential decay. (d–f) For fatty acid-modified samples where $n \geq 2$, expansion begins in localized regions that propagate, triggering expansion throughout the entire μ gel. This initiates a faster stage of expansion. The scale bar is $250 \mu\text{m}$.

uniformly at the exterior and progressed to completion with a diameter change following a first-order exponential decay at a rate similar to the control, signifying the fatty acid layer did not establish a significant ion gradient. In comparison, the μ gels modified with longer fatty acid chlorides, $n = 2$ (\times), 4 (\circ), 6 (\diamond), 8 (\oplus), 10 (dot in a diamond), 12 (\square), and 14 ($*$), were able to resist expansion for significantly longer intervals than the control, indicating the establishment of an ion gradient that was stable for some period of time. When expansion ultimately occurred, it no longer began uniformly around the exterior, nor did expansion follow a first-order exponential decay. Instead, expansion initially proceeded slowly, and there was little change in the μ gel diameter until localized regions at the μ gel surface began to swell, creating protrusions (Figure 4d–f). These isolated sites eventually propagated around the μ gel's perimeter until the entire object expanded, suggesting ion permeation was initially confined to a small defective area in the fatty acid layer.

The lifetime of the ion gradient is illustrated in Figure 5 by a plot of the half-life of μ gel expansion values, or the time interval for each modified μ gel to reach an f_b of $\ln 2$, as a function of the length of the fatty acid chloride. The time for the half-life of expansion is reported as the average of 50 trials with the uncertainty given for the 95% confidence level of the mean. The average half-lives show two distinct regions of dependence on n . The region between $n = 0$ and $n = 2$ displays a modest increase in the average half-life when the length of the fatty acid increased. The fatty acid layer formed with the shortest acid chloride ($n = 0$) did not maintain an ion gradient. The average half-life for μ gel expansion for these samples was under an hour. In great contrast, upon increasing n to 2, the half-life increased to 7 h, signifying the fatty acid layer impeded buffer ion diffusion into the μ gel matrix. In the second region between $n = 4$ and $n = 14$, the average

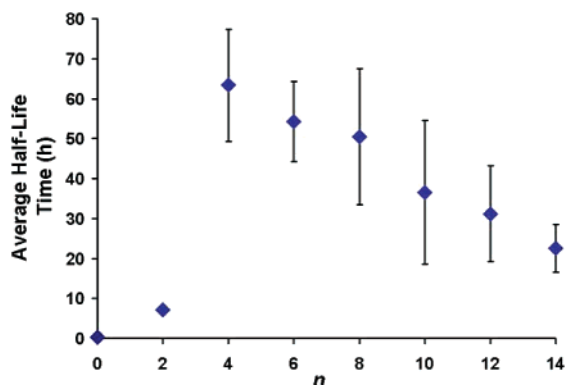


Figure 5. Average half-life of μ gel expansion (\blacklozenge) and the uncertainty range corresponding to the 95% confidence level for μ gels modified with various *n*-alkyl fatty acid chlorides ($\text{CH}_3(\text{CH}_2)_n\text{COCl}$).

half-life values were always significantly larger than those for $n \leq 2$. Surprisingly, for fatty acid chains beyond $n = 4$, a small but statistically significant decrease in half-life was observed with increasing chain length. The average half-life of expansion was greatest for samples modified with hexanoyl chloride ($n = 4$).

Variance among the individual half-life values for each chain length was much larger for the range $n = 4$ to $n = 14$, as shown in histogram form (Figure 6). All of the half-life values for μ gels modified with the two shortest fatty acid chlorides ($n = 0, 2$) were under 15 h. For layers

composed of the fatty acid chlorides with $n = 4$ to $n = 14$, the half-life of expansion values were scattered between a few hours and two weeks. However, the frequency of half-life values within the first 5 h (Figure 7) increased as the chain length increased. Localized expansion was typically observed shortly after buffer introduction for these samples, suggesting that defects on the fatty acid layer served as conduits for immediate buffer ion passage into the μ gel. Again, hexanoyl chloride-modified μ gels displayed unexpected behavior. None of these 50 samples had a half-life under 5 h, but the frequency increased to four and three samples for $n = 6$ and 8, respectively. For each set of μ gels modified with longer fatty acid chlorides ($n = 10, 12, 14$.) the frequency of half-life values under 5 h rose to 16, which is slightly larger than that acquired for μ gels modified with the much shorter fatty acid butyryl chloride ($n = 2$).

The decrease in the stability of the ion barrier with increasing chain length contrasts with previous studies of SAMs on solid surfaces. For lipid bilayers and fairly uniform monolayers of *n*-alkanethiols on gold, the ion permeability decreases as the chain length increases, which is attributed to unfavorable interactions between the ion and alkyl chains.^{10,33–37} This divergence likely stems from differences in the degree of fatty acid coverage on the μ gel surface as a function of the length of the *n*-alkyl fatty acid. For this system, the degree of coverage is expected to be influenced by the fatty acid chain density at the surface and, unlike the case for SAMs on solid

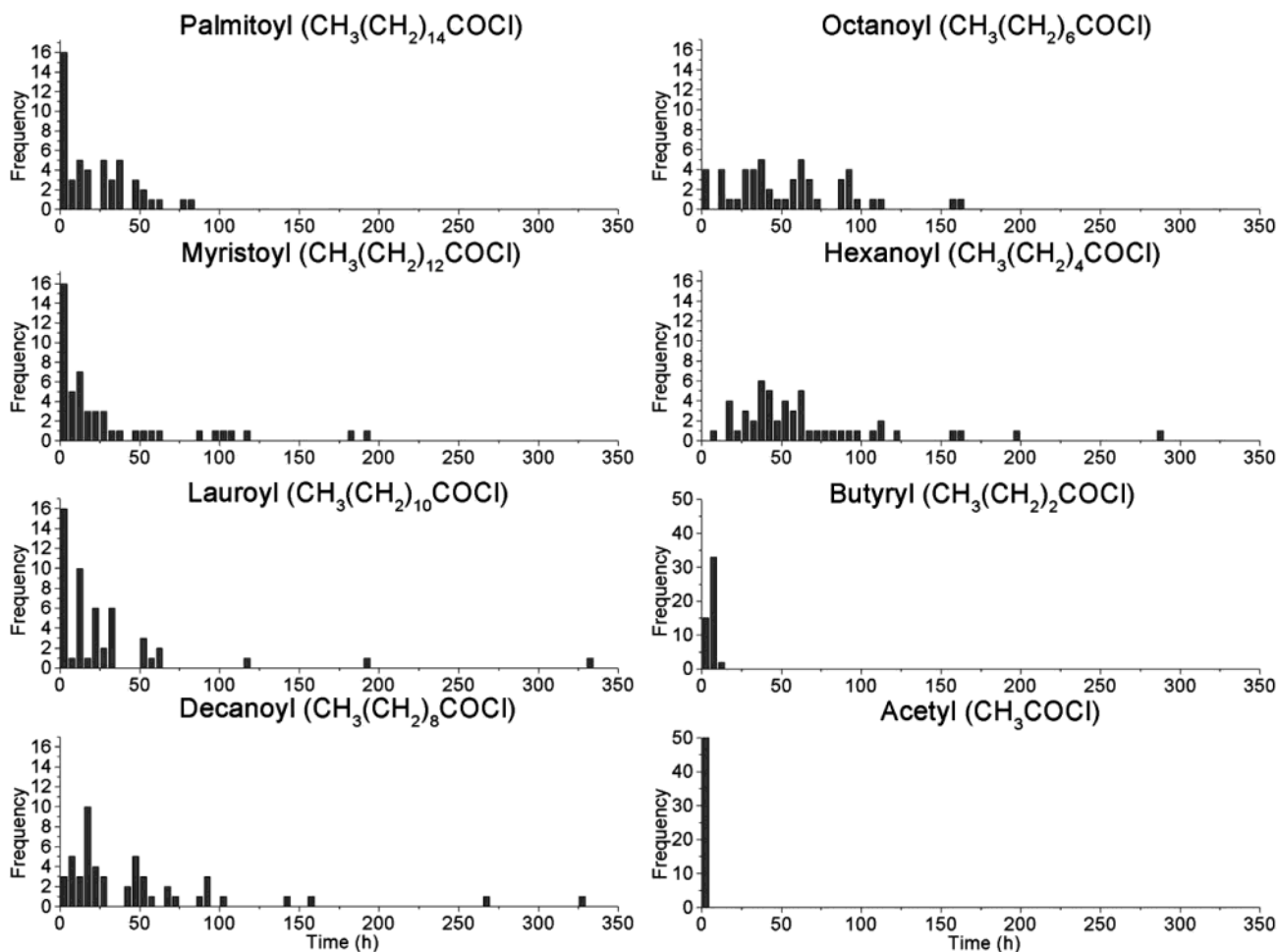


Figure 6. Histograms showing the frequency of half-life values for pH-sensitive μ gels modified with *n*-alkyl fatty acid chlorides. The number of samples with a half-life within the specified time interval (i.e., 0–5 h) is indicated.

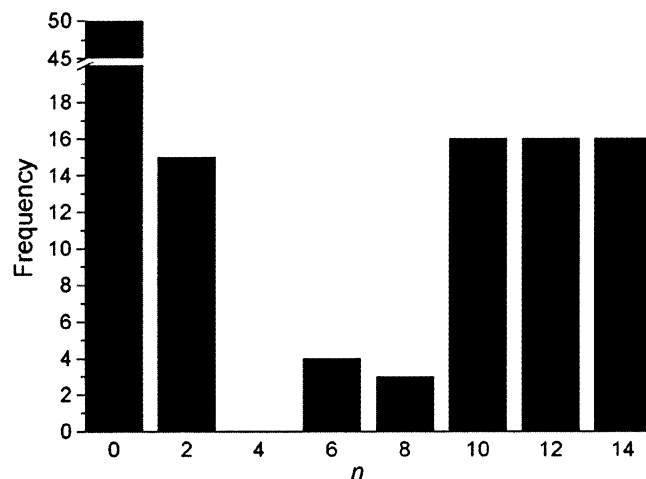


Figure 7. Histogram displaying the frequency of half-lives less than 5 h as a function of fatty acid chloride chain length chloride ($\text{CH}_3(\text{CH}_2)_n\text{COCl}$).

surfaces, by the thickness of the μgel 's perimeter functionalized with fatty acid.^{18,37} Hence, we considered the possibility that the μgel does not form an interface that is as sharp as those formed by solid substrates, leading to the esterification of μgel hydroxyl groups located deeper within the μgel matrix. Presumably, shorter acid chlorides can penetrate deeper into the hydrophilic hydrogel, resulting in the formation of a multilayered fatty acid film with an overall greater thickness than that of coatings composed of longer fatty acids. On the basis of this premise, we investigated whether the depth of fatty acid attachment on the μgel surface increased as the size of the fatty acid chloride used for modification decreased. Variation in the thickness of the hydrophobic coating between μgels modified with fatty acid chains of various lengths was explored by selectively staining the layer with a lipophilic dye (DiD) that fluoresces in nonpolar environments, denoting the location of the fatty acid layer. Examination with LSCM revealed a bright ring at the exterior of the μgels that, within the limits of resolution, did not vary significantly in thickness for the different n -alkyl fatty acid chlorides (Figure 8). We conclude that if there is a difference in the overall thickness of the fatty acid coating, it is smaller than the resolution limit of LSCM, though from these images it appears the fatty acid coatings are thicker than a monolayer.

Another explanation for the increase in permeability for longer fatty acid chlorides may be an insufficient reaction time, leading to the formation of a fatty acid coating with a low packing density. To probe this possibility, the reaction time employed to modify the μgels with palmitoyl chloride ($n = 14$) was tripled. In comparison to the case of samples modified using the standard reaction time, the mean half-life value increased only slightly and the trend of decreasing stability as the chain length increased was relatively unaffected (Figure 9). This result indicates that, for this system, extending the duration of the modification reaction does not alter the qualitative

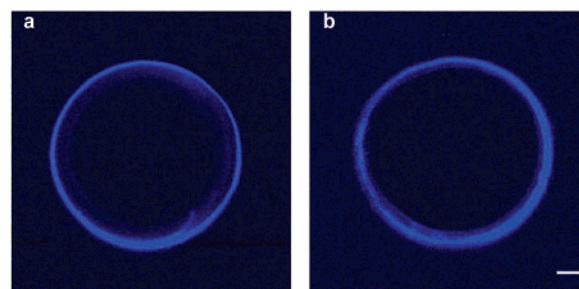


Figure 8. The fatty acid layer was selectively stained with a fluorescent lipophilic dye. A variation in the thickness of the fluorescent ring was not observed for μgels modified with fatty acid chlorides of different lengths. (a) $n = 2$; (b) $n = 12$. The scale bar is $80 \mu\text{m}$.

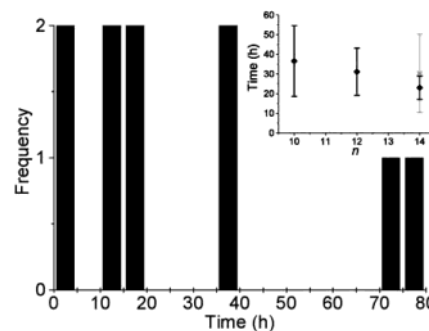


Figure 9. Frequency of half-life values for μgels modified with palmitoyl chloride (\blacksquare , $n = 14$) using an extended reaction duration of 27 h. The mean values for the standard (\blacklozenge) and extended reaction times ($*$) with the 95% confidence level are indicated in the inset.

trend of decreasing half-life values as the chain length increases.

Discord between the influence of the chain length on ion permeability for SAMs on solid surfaces and the system reported in this study suggests that utilization of a hydrogel substrate introduces additional factors that influence permeability. Although we were unable to unequivocally identify these factors, we believe the use of a hydrogel substrate leads to the formation of an insulating layer that varies in surface coverage as a function of the acid chloride length. The μgel may not form a sharp interface with the modification solution, leading to a chain length dependent variation in the depth of the hydrogel shell esterified by fatty acids. As discussed, this variation must be smaller than the detectable limit of LSCM. Additionally, the potential effect of the increased surface roughness for hydrogel substrates compared to conventional solid surfaces warrants consideration. Increased surface roughness is known to decrease interchain order, increase the structural defect frequency, and lower the surface coverage of SAMs.³⁷ The fatty acid μgel coatings are likely beset with these features, and the surface roughness may interfere more strongly in well-packed layer formation for longer fatty acid chains. One can envision that the initial attachment of fatty acids to the μgel exterior shields the neighboring substrate from subsequent reaction with other fatty acid chlorides. Consequently, the surface coverage decreases as the chain length increases, so shorter chains would form denser fatty acid coatings and a higher frequency of pinhole defects would be present when longer fatty acids were employed. This is consistent with the reported experimental observations. A layer composed of the shortest chains was unable to maintain an ion gradient, but increasing the chain length decreased the ion permeation until a length

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of $n = 4$ was reached, after which the occurrence of defects in the fatty acid layer dominated permeability properties. Exploration of these hypotheses using model systems based on planar hydrogel substrates is underway.

Summary

Half-life of expansion values were acquired for μ gels modified with saturated n -alkyl fatty acid chlorides. The permeability of the resulting fatty acid layers to buffer ions does not decrease as the alkyl chain length increases, as observed for SAMs on solid surfaces. The average half-life value is at a maximum when $n = 4$, indicating the highest resistance to buffer ion-induced expansion; then it decreases as the chain length increases. This contrasting

trend is likely caused by layer formation on the hydrogel substrate, which may introduce additional facets that activate a defect-dominated assembly process that has a greater influence on the ion permeability of the fatty acid layer than the alkyl chain length. Further investigation is necessary to elucidate these factors.

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