

Acid-Degradable Protein Delivery Vehicles Based on Metathesis Chemistry

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In this communication we demonstrate that acyclic diene metathesis (ADMET) polymerization is a powerful methodology for the synthesis of acid-degradable polymers based on polyketals and polyacetals. Ten new polyketals and polyacetals were synthesized, using ADMET, and a polyacetal based on anthracene aldehyde was identified, which had the physical properties needed for microparticle formulation. The antioxidant protein catalase was encapsulated into microparticles, formulated from this polyacetal, using a double emulsion procedure, and cell culture studies demonstrated that these microparticles dramatically improved the ability of catalase to scavenge hydrogen peroxide produced by macrophages. We anticipate numerous applications of ADMET for the synthesis of acid-degradable polymers based on its excellent tolerance toward functional groups and ease of synthesis.

1. Introduction

Macrophages play a central role in chronic inflammatory diseases, and there is thus great interest in targeting anti-inflammatory therapeutics to macrophages.^{1–3} Catalase is an anti-inflammatory enzyme that detoxifies hydrogen peroxide and has shown tremendous efficacy in treating animal models of inflammatory disease. Unfortunately, catalase has been ineffective in clinical trials, due to delivery problems, and delivery vehicles that can enhance its efficacy are greatly needed. Microparticles based on biodegradable polymers have considerable potential for improving the efficacy of catalase, due to their ability to efficiently target macrophages, and because of their excellent biocompatibility and shelf life.⁴ However, polymeric microparticles are predominantly formulated from polyesters, which can be problematic for the treatment of chronic inflammatory diseases due to their acidic degradation products and slow hydrolysis kinetics.⁵

Polyacetals and polyketals are two new classes of polymers that have considerable potential as drug carriers for the treatment of chronic inflammatory diseases. Polyacetals and polyketals degrade into alcohols and aldehydes/ketones and may avoid the inflammatory problems associated with the acidic degradation products of polyesters. Acetals and ketals are more sensitive to the acidic environment of tumors and phagosomes than esters and hydrazones but are more stable than these linkages in the pH 7.4 environment of the blood.^{6–9} Polyacetals and polyketals also have the potential to disrupt phagosomes, by selectively degrading in the phagosome and osmotically destabilizing it. Although polyacetals and polyketals have potential for drug delivery, synthetic challenges have limited their potential applications. The common methods for synthesizing polyketals and polyacetals are either through the acetal exchange reaction or through condensation reactions between vinyl ethers and alcohols.¹⁰ Both of these methodologies have limited tolerance to functional groups, and thus new strategies for synthesizing polyketals and polyacetals are greatly needed. Interestingly,

acyclic diene metathesis (ADMET) polymerization has also been once reported for the synthesis of a polyacetal, based on benzaldehyde acetal.¹¹ Although this polyacetal was a viscous solid, which lacked the physical properties needed for microparticle formation, ADMET warrants greater investigation for the synthesis of polyketals and polyacetals, because of its excellent tolerance to functional groups.^{12–14}

In this communication, we demonstrate that ADMET is a robust strategy for the synthesis of polyacetals and polyketals. Ten new polyacetals and polyketals were synthesized using ADMET, and a polyacetal based on anthracene aldehyde was identified, which could be formulated into microparticles. Catalase was encapsulated into microparticles composed of this polyacetal, and cell culture experiments demonstrated that these microparticles dramatically improved the ability of catalase to scavenge hydrogen peroxide produced by macrophages.

2. Experimental Section

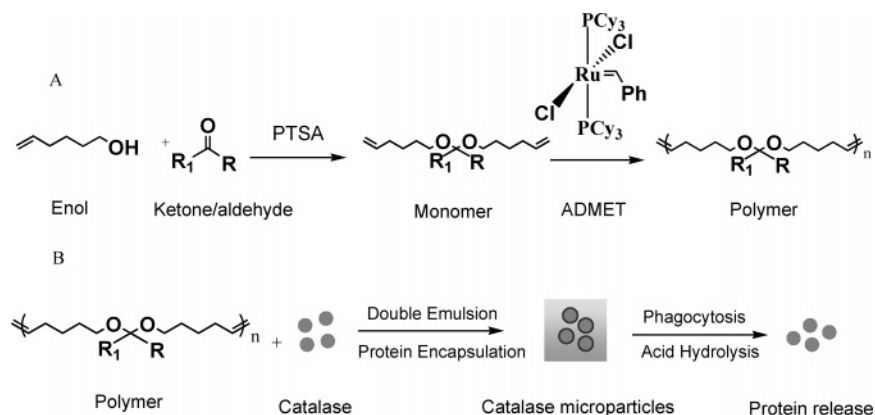
2.1. Materials. All chemicals were purchased from Sigma-Aldrich (St. Louis, MO) and used as received unless otherwise specified. Benzene and 2,2-dimethoxypropane were purified by distillation; *p*-toluenesulfonic acid (PTSA) was recrystallized before use. ¹H NMR spectra were taken on a Varian Mercury V_X 400. Gel permeation chromatography measurements were made using a Shimadzu SCL-10A, based on polystyrene standards obtained from Polymer Laboratories (1060 *M_w*, 20.8 min; 2970 *M_w*, 19.0 min; 10 800 *M_w*, 16.5 min). Ultraviolet spectroscopy measurements were performed using a Shimadzu UV-vis spectrophotometer (1700-Pharmaspec). Microparticles were formulated using a Fisher PowerGen model 500 homogenizer (Fisher Scientific). Scanning electron microscopy (SEM) images were taken using a Hitachi S-800 instrument. RAW macrophages were purchased from the American Type Culture Collection (ATCC) and cultured according to their described protocols.

2.2. Monomer Synthesis. The ADMET monomers **1a–10a** were synthesized according to the general procedure described below to synthesize monomer **8a**.

Bis(*but-3-enyloxy-methyl*)-*9-anthracene* (**8a**). 9-Anthracene aldehyde (29 mmol) and 3-buten-1-ol (86 mmol) were added to a 250 mL round-bottom flask at 0 °C, which contained 100 mL of dry tetrahydrofuran (THF) and 5 g of vacuum-dried 5 Å molecular sieves. PTSA (1.5 mmol)

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Scheme 1. (A) Synthesis of Polyketals/Polyacetals Using ADMET and (B) Formulation of Catalase-Loaded Microparticles by w/o/w Double Emulsion^a

^a Microparticles degrade in the phagosome after phagocytosis by macrophages.

was added to this solution, and the mixture was stirred at room temperature for 8 h, quenched with triethylamine, filtered, extracted with methylene chloride, and purified by silica gel chromatography, using ethyl acetate/hexane/triethylamine as the eluent, generating **8a** with a yield of 73%. ¹H NMR (CDCl₃): δ 8.72 (d, 2H, *J* = 8.78 Hz), 8.43 (s, 1H), 7.97 (d, 2H, *J* = 8.78), 7.46 (m, 4H), 6.74 (s, 1H), 5.79 (m, 2H), 5.01 (m, 4H), 3.86 (m, 2H), 3.53 (m, 2H), 2.35 (m, 4H). ¹³C NMR (CDCl₃): δ 134.96, 131.45, 129.69, 128.72, 125.79, 124.62, 116.45, 101.44, 67.55, 34.83. HRMS (ESI) Calcd for C₂₃H₂₄O₂ [M]⁺: 332.1776. Found: 332.1764.

Acetone Dihex-5-enyl Ketal (1a). ¹H NMR (CDCl₃): δ 5.81 (m, 2H), 4.98 (m, 4H), 3.39 (t, *J* = 7.14, 4H), 2.07 (q, *J* = 7.14, 13.73 Hz, 4H), 1.51–1.60 (m, 4H), 1.40–1.49 (m, 4H), 1.34 (s, 6H). ¹³C NMR (CDCl₃): δ 138.57, 114.41, 99.41, 60.45, 33.77, 29.87, 25.79, 25.00. Yield of **1a**: 78%. Anal. calcd for C₁₅H₂₈O₂: C, 74.94; H, 11.74. Found: C, 74.87; H, 11.95.

Acetone Dipent-4-enyl Ketal (2a). ¹H NMR (CDCl₃): δ 5.83 (m, 2H), 5.04–4.94 (m, 4H), 3.38 (t, *J* = 6.88 Hz, 4H), 2.10 (m, 4H), 1.64 (m, 4H), 1.34 (m, 6H). ¹³C NMR (CDCl₃): δ 138.80, 114.14, 99.44, 60.68, 46.07, 30.10. Yield of **2a**: 70%. Anal. calcd for C₁₃H₂₄O₂: C, 74.92; H, 11.39. Found: C, 74.92; H, 11.84.

Acetone Dibut-3-enyl Ketal (3a). ¹H NMR (CDCl₃): δ 5.83 (m, 2H), 5.03 (m, 4H), 3.45 (t, *J* = 7.32, 4H), 2.27 (q, *J* = 6.59, 13.91 Hz, 4H), 1.33 (s, 6H). ¹³C NMR (CDCl₃): δ 135.49, 116.09, 99.64, 60.09, 34.57, 25.23. Yield of **3a**: 76%. Anal. calcd for C₁₁H₂₀O₂: C, 71.69; H, 11.02. Found: C, 71.54; H, 11.08.

Cyclohexanone Dihex-5-enyl Ketal (4a). ¹H NMR (CDCl₃): δ 5.82–5.92 (m, 2H, 2-CH), 4.95–5.05 (m, 4H 2CH₂), 3.39 (t, *J* = 7.2 Hz, 4H, OCH₂), 2.07–2.15 (m, 4H 2CH₂), 1.38–1.69 (m, 18H, 9CH₂). ¹³C NMR (CDCl₃): δ 138.84, 114.4, 99.8, 59.2, 33.7, 29.6, 25.7, 22.9. Yield of **4a**: 81%. HRMS (ESI) Calcd for C₁₈H₃₂O₂ [M]⁺: 280.2402. Found: 280.2395.

2-Bis(3-butenyloxymethyl)-1-chloropropane (5a). ¹H NMR (CDCl₃): δ 5.84 (m, 2H), 5.08 (m, 4H), 3.50 (m, 6H), 2.31 (q, *J* = 6.59, 13.91 Hz, 4H), 1.42 (s, 3H). ¹³C NMR (CDCl₃): δ 134.97, 116.46, 100.09, 60.56, 46.35, 34.25, 21.21. Yield of **5a**: 92%. Anal. calcd for C₁₁H₁₉O₂Cl: C, 60.38; H, 8.75. Found: C, 60.62; H, 8.94.

4-O-Benzylcyclohexanone-dihex-5-enyl Ketal (6a). ¹H NMR (CDCl₃): δ 7.33 (m, 5H), 5.81 (m, 4H), 4.97 (m, 4H), 4.53 (s, 2H), 3.47 (m, 1H), 3.38 (dt, *J* = 2.19, 6.59, 8.79 Hz, 4H), 2.07 (m, 4H), 1.93 (m, 2H), 1.79 (m, 2H), 1.65 (m, 2H), 1.53 (m, 10H). ¹³C NMR (CDCl₃): δ 138.49, 128.16, 127.39, 114.54, 99.34, 74.99, 70.12, 59.60, 33.69, 29.99, 28.05, 25.71. Yield of **6a**: 72%. HRMS (ESI) Calcd for C₂₅H₃₈O₃ [M]⁺: 386.2821. Found: 386.2831.

4,4-Bis-pent-4-enyloxy-tetrahydropyran (7a). ¹H NMR (CDCl₃): δ 5.80 (m, 2H), 4.98 (m, 4H), 3.68 (m, 4H), 3.38 (t, *J* = 5.86 Hz, 4H), 2.08 (m, 4H), 1.78 (m, 4H), 1.56 (m, 4H), 1.47 (m, 4H). ¹³C NMR (CDCl₃): δ 138.67, 114.32, 64.64, 59.39, 45.95, 34.25, 29.38, 25.30.

Yield of **7a**: 68%. HRMS (ESI) Calcd for C₁₇H₃₈O₃ [M]⁺: 282.2195. Found: 282.2159.

Bis(5-hexenyloxy) 2-Naphthaldehyde (9a). ¹H NMR (CDCl₃): δ 7.94 (s, 1H), 7.85 (m, 3H), 7.57 (m, 1H), 7.48 (m, 2H), 5.81 (m, 2H), 5.66 (s, 1H), 4.97 (m, 4H), 3.54 (m, 4H), 2.07 (m, 4H). ¹³C NMR (CDCl₃): δ 135.83, 135.11, 133.13, 132.74, 128.05, 127.75, 127.46, 124.29, 116.30, 101.26, 64.52, 34.19. Yield of **9a**: 70%. HRMS (ESI) Calcd for C₁₉H₂₂O₂ [M]⁺: 282.1619. Found: 282.1619.

1-Bis(3-butenyloxy)-1,3-diphenyl-2-propenone (10a). ¹H NMR (CDCl₃): δ 7.55 (m, 2H), 7.35 (m, 8H), 6.87 (d, *J* = 16 Hz, 1H), 6.12 (d, *J* = 16 Hz, 1H), 5.87 (m, 2H), 5.07 (m, 4H), 3.53 (m, 2H), 3.36 (m, 2H), 2.38 (m, 4H). ¹³C NMR (CDCl₃): δ 141.45, 135.59, 131.71, 130.72, 128.30, 127.81, 127.54, 126.73, 126.55, 116.11, 100.73, 60.80, 34.50. Yield of **10a**: 55%. HRMS (ESI) Calcd for C₂₃H₂₆O₂ [M]⁺: 334.1932. Found: 334.1942.

2.3. Polymer Synthesis. The polymers **1b–10b** were synthesized, using ADMET, according to the general procedure described below to synthesize polymer **8b**.

Poly(bis(but-3-enyloxy-methyl)-9-anthracene (8b). Dried monomer **8a** (0.8 g, 2.40 mmol) was placed in a 50 mL round-bottom two-neck flask equipped with a stir bar and reflux condenser. The Grubbs generation I catalyst (Cy₃P)₂(Cl)₂Ru=CHPh (0.039 g, 0.048 mmol), was added to the reaction flask, and the mixture was placed in an oil bath and heated to 60 °C under high vacuum (<10⁻³ mmHg) for 24 h (50:1 monomer to catalyst ratio). The mixture was cooled and quenched by exposing it to air, and the resulting polymer (**8b**) was purified by silica gel chromatography, using ethyl acetate/hexane as the eluent. ¹H NMR (CDCl₃): δ 8.69 (s, 2H), 8.41 (s, 1H), 7.94 (s, 2H), 7.42 (s, 4H), 6.68 (s, 1H), 5.37 (s, 2H), 3.76 (s, 4H), 2.32 (s, 4H).

Poly(acetone dihex-5-enyl ketal) (1b). ¹H NMR (CDCl₃): δ 5.38 (s, 2H), 3.37 (s, 4H), 1.98 (s, 4H), 1.52 (s, 4H), 1.30 (s, 10).

Poly(acetone dipent-4-enyl ketal) (2b). ¹H NMR (CDCl₃): δ 5.46 (s, 2H), 3.37 (m, 4H), 2.20 (s, 4H), 1.64 (s, 4H), 1.34 (s, 6H).

Poly(acetone dibut-3-enyl ketal) (3b). ¹H NMR (CDCl₃): δ 5.48 (s, 2H), 3.39 (s, 4H), 2.20 (s, 4H), 1.33 (s, 6H).

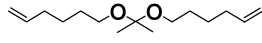
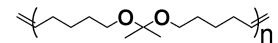
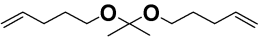
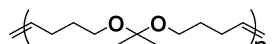
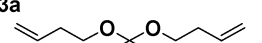
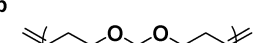
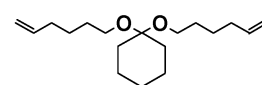
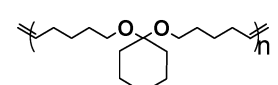
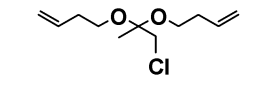
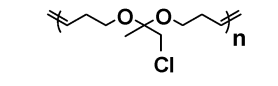
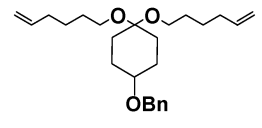
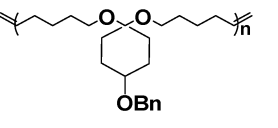
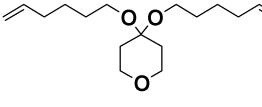
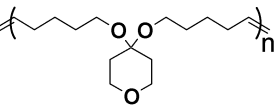
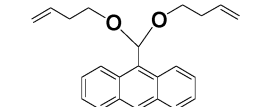
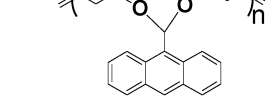
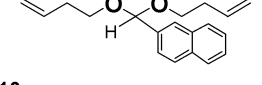
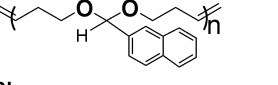
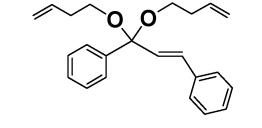
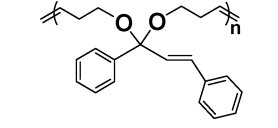
Poly(cyclohexanone dihex-5-enyl ketal) (4b). ¹H NMR (CDCl₃): δ 5.38 (s, 2H), 3.37 (m, 4H), 2.00 (s, 4H), 1.22–1.68 (s, 18).

Poly(2-(bis(3-butenyloxymethyl)-1-chloropropane)) (5b). ¹H NMR (CDCl₃): δ 5.52 (s, 2H), 3.46 (s, 6H), 2.27 (s, 4H), 1.42 (s, 3H).

Poly(4-O-benzylcyclohexanone-dihex-5-enyl ketal) (6b). ¹H NMR (CDCl₃): δ 7.34 (s, 5H), 5.37 (s, 2H), 4.52 (s, 2H), 3.47 (s, 1H), 3.36 (m, 4H), 1.97 (m, 6H), 1.78 (s, 2H), 1.65 (m, 2H), 1.52 (m, 6H), 1.39 (m, 4H).

Poly(4,4-bis-pent-4-enyloxy-tetrahydropyran) (7b). ¹H NMR (CDCl₃): δ 5.40 (s, 2H), 3.66 (s, 4H), 3.37 (s, 4H), 2.02 (s, 4H), 1.77 (s, 4H), 1.55 (s, 4H), 1.37 (s, 4H).

Table 1. Polyacetals and Polyketals Synthesized Using ADMET

entry	monomer	polymer	M_n	polydispersity	physical state
1	1a 	1b 	8275	1.13	liquid
2	2a 	2b 	8434	2.23	liquid
3	3a 	3b 	9755	2.04	liquid
4	4a 	4b 	11 298	1.15	liquid
5	5a 	5b 	6490	2.14	liquid
6	6a 	6b 	12 530	1.18	liquid
7	7a 	7b 	4875	2.16	liquid
8	8a 	8b 	4880	1.40	solid
9	9a 	9b 	7660	2.12	liquid
10	10a 	10b 	6780	1.45	solid

Poly(bis(5-hexenyloxy) 2-naphthaldehyde) (9b). $^1\text{H NMR}$ (CDCl_3): δ 7.96 (s, 1H), 7.82 (m, 3H), 7.60 (m, 1H), 7.45 (s, 1H), 5.63 (s, 1H), 5.40 (s, 2H), 3.48 (m, 4H), 2.10 (s, 4H), 1.64 (s, 4H), 1.42 (s, 4H).

Poly(1-bis(3-butenyloxy)-1,3-diphenyl-2-propenone) (10b). $^1\text{H NMR}$ (CDCl_3): δ 7.52 (s, 2H), 7.27 (s, 10H), 6.85 (m, 1H), 6.08 (s, 1H), 5.51 (s, 2H), 3.45 (s, 2H), 3.30 (s, 2H), 2.32 (s, 4H).

2.4. Cell Toxicity of Microparticles Composed of 8b. A 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) reduction assay was performed with microparticles composed of **8b** to determine their toxicity. RAW 264.7 cells were seeded at a density of 1×10^5 cells/well and incubated in 96 well plates for 24 h. Cells were treated with microparticles at various particle concentrations (100 ng/mL to 1 mg/mL) and incubated for various durations (0.5–24 h). Next, 20 μL of an MTT solution (5 mg/mL in PBS) was added to each well, the

cells were incubated for 2 h, and 200 μL of dimethyl sulfoxide (DMSO) was added to the cells to dissolve the resulting formazan crystals. After 10 min of incubation, the absorbance at 585 nm was measured using an Emax microplate reader (Molecular Devices, Sunnyvale, CA). Percentage cell viability was calculated by comparing the absorbance of the control cells to that of microparticle-treated cells.

2.5. Measurement of Hydrogen Peroxide Production from Macrophages. The Amplex Red assay was used to detect the release of H_2O_2 from RAW 264.7 macrophages. Cells treated with microparticles were washed three times with Krebs–Ringer bicarbonate buffer (pH 7.4), obtained from Sigma-Aldrich (St. Louis, MO). Exactly 100 μL of a Krebs–Ringer bicarbonate buffer (pH 7.4) solution, containing 50 μM 10-acetyl-3,7-dihydroxyphenoxazine and 0.1 U/mL horseradish peroxidase (HRP), prewarmed at 37 $^\circ\text{C}$, was added to the cells (grown

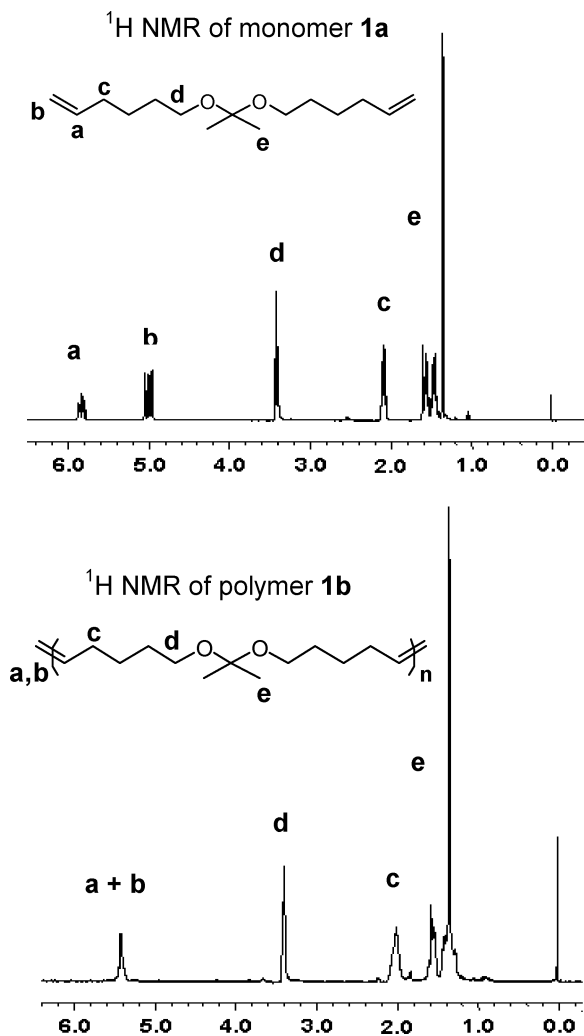


Figure 1. ¹H NMR spectra of monomer **1a** and polymer **1b**. Shifts of vinyl peaks (a and b) demonstrate acyclic diene metathesis polymerization.

in a 96 well plate). After a 2 h incubation period, at 37 °C, the fluorescence of the cells was measured using a microplate reader, with excitation at 530 nm and emission at 590 nm.

3. Results and Discussion

3.1. Monomer and Polymer Synthesis. In this report we investigated the ability of ADMET to synthesize polyketals and polyacetals for drug delivery. The monomers and resulting

polyacetals and polyketals are summarized in Table 1. The monomers were synthesized via condensation of an aldehyde or ketone with various ene-1-ols, in freshly distilled THF, using PTSA as a catalyst. These monomers were polymerized using the Grubbs generation I catalyst, $\text{Cl}_2(\text{PCy}_3)_2\text{Ru}(=\text{CHPh})$, at 60 °C for 24 h under vacuum. The polymerization yields were determined by comparing the ¹H NMR peak positions of the vinyl hydrogens before and after polymerization and were in general greater than 95%, as shown in Figure 1; polymers were analyzed without purification. The polymer molecular weights generated by ADMET were between 5 and 12 kD, which is expected, due to the step growth nature of ADMET.^{15–17} Most of the polyketals and polyacetals synthesized were pastes; however, polymers synthesized from **8a** and **10a** were solids and thus could be potentially used for microparticle formulation. The hydrolysis half-life of **8a** was investigated by UV spectroscopy in 90% dioxane + 10% aqueous buffer at 37 °C and was determined to be pH-sensitive, having half-lives of 3 days at pH 4.5 and 20 days at pH 7.4.¹⁸ The hydrolysis of **8a** is significantly slower than that of other benzaldehyde acetals used in drug delivery; this is most likely caused by the greater hydrophobicity of **8a**.¹⁸ The polyacetal **8b**, which was generated from **8a**, was chosen for further investigation as a scaffold for microparticle formulation because of its solid, crystalline nature and pH sensitivity.

3.2. Formulation of Catalase-Loaded Microparticles.

Microparticles were formulated from the polymer **8b**, which encapsulated the protein catalase. Briefly, a 100 μL aqueous solution of catalase (100 mg/mL) was dispersed by homogenization (21 500 rpm, 30 s) into 1.0 mL of methylene chloride, containing 100 mg of **8b**, generating a water-in-oil (w/o) emulsion. This w/o emulsion was then dripped into 5 mL of an 8% (w/v) aqueous polyvinyl alcohol (PVA) solution and was stirred with a homogenizer at 24 200 rpm for 1 min. The resulting w/o/w emulsion was then poured into 25 mL of pH 7.4 buffer and was stirred for several hours, thus evaporating the methylene chloride. The resulting particles were isolated by centrifugation and freeze-dried, generating a white solid powder. The protein encapsulation efficiency of this process was 30%, as determined by UV absorbance at 280 nm, and generated microparticles (termed catalase microparticles) that had 30 μg of protein per milligram of polymer.¹⁹ A SEM image of the catalase microparticles, shown in Figure 2, demonstrates that they are 0.5–3 μm in diameter. The average size of these particles was calculated to be $1.76 \pm 0.48 \mu\text{m}$ using the Statistical Package for Social Sciences (SPSS) software. Although the size distribution of these particles is polydisperse, they still should be suitable for drug delivery to macrophages,

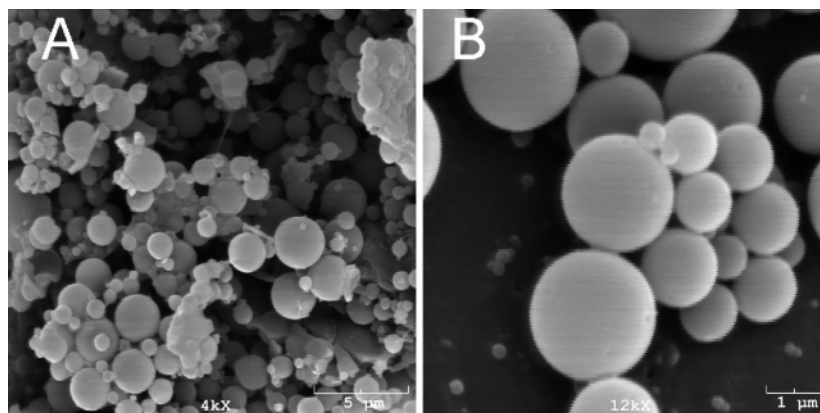


Figure 2. SEM images of catalase-loaded microparticles. Scale bar: (A) 5 μm , (B) 1 μm . SEM images were taken on a Hitachi S-800.

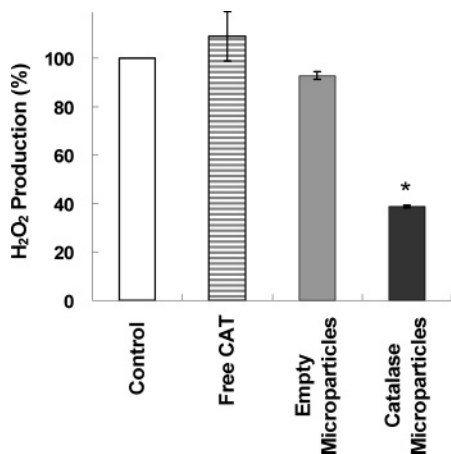


Figure 3. Catalase microparticle enhancement of delivery of catalase to macrophages. Macrophages were incubated with catalase microparticles (black bar), empty microparticles (gray bar), free catalase (horizontal stripe), and media only (white bar). For statistical analysis, three independent wells were measured for each sample. Significance of results was determined via the *t*-test with $p < 0.05$.

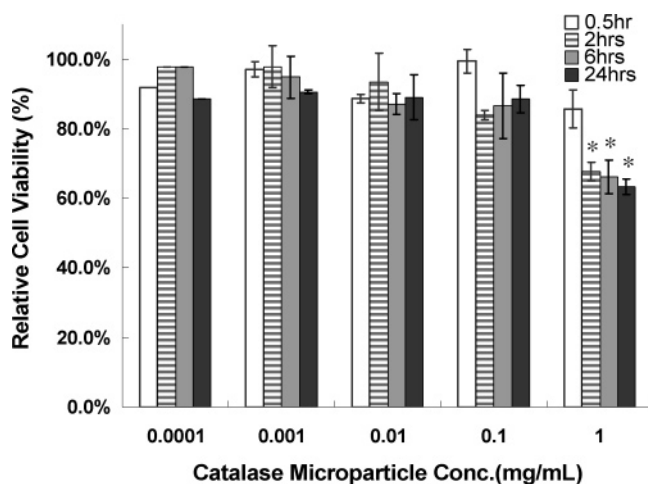


Figure 4. Microparticles composed of **8b** showing minimal toxicity: 0.5 h (white bar); 2 h (horizontal stripe); 6 h (gray bar); 24 h (black bar). For statistical analysis, three independent cell viabilities were measured for each sample. Significance of results was determined via the *t*-test with $p < 0.005$.

as macrophages readily phagocytose particles in the 0.5–3 μm range.

3.3. Inhibition of Hydrogen Peroxide Production by Catalase Microparticles. The ability of catalase microparticles to scavenge hydrogen peroxide produced from macrophages was investigated in cell culture. RAW 264.7 macrophages (1×10^5 cells/well, 96 well plate) were incubated with either 0.1 mg/mL catalase microparticles (3 μg of catalase in 0.1 mg of microparticles), free catalase (3 $\mu\text{g}/\text{mL}$ catalase), or 0.1 mg/mL of empty microparticles for 2 h and then stimulated with 0.2 $\mu\text{g}/\text{mL}$ phorbol myristate acetate (PMA) for 4 h. The hydrogen peroxide production from these macrophages was then measured by the Amplex Red assay kit (Invitrogen, Amplex Red kit A22188, Carlsbad, CA), using the protocol provided in the kit (see Experimental Section). Figure 3 demonstrates that encapsulating catalase into microparticles composed of **8b** dramatically improves its efficacy. Free catalase by itself (horizontal stripes) causes very little inhibition of hydrogen peroxide production, whereas catalase microparticles (black bar) induce a 60% reduction in hydrogen peroxide production. Empty microparticles, composed of **8b**, had a minimal effect on hydrogen peroxide production and showed little toxicity at the

concentrations used in this experiment, as determined by an MTT assay (Figure 4).

4. Conclusions

In this communication we have demonstrated that ADMET is a powerful strategy for the synthesis of acid-degradable microparticles based on polyacetals and polyketals. Several polyacetals and polyketals were synthesized, using ADMET, and a polyacetal composed of an anthracene acetal was identified that had the properties needed for microparticle formulation. The therapeutic protein catalase was encapsulated into anthracene-based microparticles, 1–3 μm in size, using a double emulsion procedure. In cell culture experiments, these microparticles significantly improved the ability of catalase to scavenge hydrogen peroxide generated by macrophages. We anticipate widespread interest in ADMET-based microparticles for drug delivery, based on their acid sensitivity, ease of synthesis, and cell culture efficacy.

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