

Use of Cationic Aerosol Photopolymerization To Form Silicone Microbeads in the Presence of Molecular Templates

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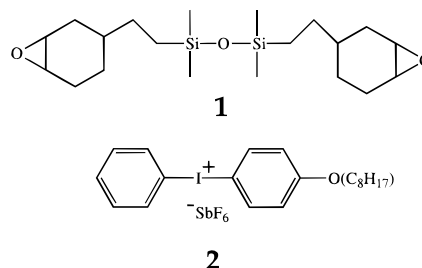
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A new methodology for template-directed polymerization is described which is suitable for easy microbead formation. Cationic polymerization of a bis-epoxy silicone monomer by a diaryliodonium salt photoinitiator was found to occur fast enough to polymerize the droplets of an aerosol spray of the monomer, photoinitiator, and template in flight. Symmetric microbeads averaging 31 μm in diameter were produced and captured by electrostatic precipitation. The effect of numerous functional groups on the rate of polymerization is discussed. Nitrogenous bases were found to be detrimental to polymer bead formation, as were certain carboxylic acids. Beads imprinted with morphine analogue thebaine displayed stronger molecular recognition properties for thebaine than did nonimprinted beads. However, both thebaine-templated and nonimprinted beads retained similar amounts of the thebaine derivative 17,18-bis(methoxycarbonyl)-6,14-ethenocodeine methyl ether.

Introduction

As part of the ongoing search for man-made macromolecular systems which can perform feats of specific molecular recognition,¹ a great deal of research has gone into the design of template-imprinted polymers. The construction of these selective cavities is accomplished by the self-assembly of "host" monomers in a complementary manner about a "guest" template molecule. Potential uses for these materials include highly specific chromatography media, medicinal release agents, chemical sensors, and as a replacement for catalytic antibodies. These preorganization interactions create an energy-minimized structure which, after polymerization, retains the position of functional groups responsible for these interactions, even after removal of the template. There are two major methods currently used to generate shape-specific cavities: The method favored by Wulff and co-workers² involves coupling their template molecules to polymerizable groups through weak covalent bonds. After polymerization, these bonds can be selectively cleaved leaving a preoriented set of functional groups flanking a shape-specific cavity. The rigidity of the polymer matrix keeps the crucial functional groups in correct orientation to interact with the desired substrate molecule. A second method, presented by Mosbach,^{1a} relies on a variety of noncovalent interactions between monomer and template to preorganize the monomers so that they generate a selective binding site in the final polymer matrix. The preorganization step is dependent upon complementary dipole–dipole dispersion forces, hydrogen bonding, and assorted other electrostatic interactions.^{1a}

Historically, template imprinting of organic polymers typically involves radical polymerization of monomers and cross-linkers of the methyl methacrylic acid and divinylbenzene classes, respectively, with AIBN as the initiator.³ Presented herein are the preliminary results of a study of cationic aerosol polymerization for use in generating template-imprinted polymers. This technique uses 1,3-bis[2-(3-{7-oxabicyclo[4.1.0]heptyl})ethyl]-tetramethyldisiloxane (**1**) as both monomer and cross-



linker and (4-(octyloxy)phenyl)phenyliodonium hexafluoroantimonate (**2**) as a cationic photoinitiator as described by Crivello and Lee.⁴ This monomer/initiator system was found to undergo exceedingly fast cationic polymerization upon exposure to UV light (Scheme 1). DSC photocalorimetry studies on the epoxysilicone monomer/diaryliodonium photoinitiator thin-film rate of cationic polymerization revealed completed reactions in under 30 s.⁴ In our hands, cationic aerosol polymerization of bis-epoxy silicone **1** was complete in under 1 s during microbead production.

Whereas the free radical polymerization processes mentioned earlier are capable of generating shape-specific polymeric materials, large-scale synthesis of such products involves drawbacks which are not present for a cationic polymerization method. Free radical

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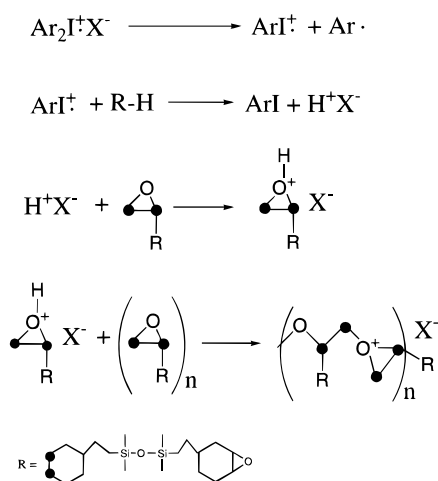
(1) For some recent reviews of template-imprinted polymers see: (a) Mosbach, K. *Trends Biochem. Sci.* **1994**, *19*, 9. (b) Sellergren, B. *J. Chromatogr. A* **1994**, *673*, 133. (c) Sellergren, B.; Shea, K. *J. Chromatogr.* **1993**, *635*, 31.

(2) Wulff, G.; Poll, H.; Minarik, M. *J. Liquid Chromatogr.* **1986**, *9*, 385.

(3) Ramstrom, O.; Nicholls, I.; Mosbach, K. *Tetrahedron: Asym.* **1994**, *5*, 649.

(4) Crivello, J.; Lee, J. *J. Polym. Sci.: Part A: Polym. Chem.* **1990**, *28*, 479.

Scheme 1



polymerization must be done under an inert atmosphere to prevent quenching of the reaction by O_2 , and when used to produce imprinted polymers, it is usually performed in organic solvents.¹ These solvents impart a porosity to the polymeric material. Cationic polymerization is not affected by the presence of atmospheric oxygen and uses no solvent. The template and photoinitiator are dissolved directly in the monomer. The monomer and photoinitiator themselves were studied for toxicity and both are known to be quite safe.⁵ The speed of aerosol microbead generation by the system allows production of material faster than the traditional technique of irradiating a sample for several hours, then grinding and sifting the resultant block down into microbead sized particles.

Results and Discussion

Functionalities Affecting Polymerization. It is known that certain functionalities can interfere with cationic polymerization. To what extent they actually interfered with the template-directed cationic polymerization had to be determined and so a systematic study of these potential limitations was initiated. In this investigation, the compatibility of various functional groups with the polymerization system was examined via a simple test. The test protocol involved spreading a mixture of monomer, photoinitiator (0.5 mol %), and a test molecule between two salt plates and recording an IR spectrum. The salt plates were then exposed to UV light for a period of time ranging from 10 s to 10 min, with checks for polymerization roughly every 30 s (polymerization was assumed to occur when the two salt plates became "glued" together). At this point the IR spectrum was again acquired and compared to the spectrum taken before exposure to UV light and to the IR spectrum of the test molecule alone to determine if there had been any change in the test molecule structure. The results of these tests can be found in Table 1. Untemplated monomer/photoinitiator results were used as a reference. Polymer imprinted with trinitrobenzene (2.7 mol %) formed in under 5 min and showed no change in the template structure. Rate attenuation of the polymerization step can be explained by the nitro

Table 1. Effect of Functional Groups on Polymerization

| template | molar ratio ^a | polymerize? | IR change? | rate |
|----------------------------------|--------------------------|-------------|------------|--------|
| 1. diphenylmethylphosphine oxide | 1 to 33 | yes | no | 7 min |
| 2. trinitrobenzene | 1 to 37 | yes | no | 5 min |
| 3. pyridine | 1 to 12 | yes | no | 10 min |
| 4. 3,5-dimethylpyrazole | 1 to 10 | yes | no | 7 min |
| 5. dimethylformamide | 1 to 100 | yes | no | 10 min |
| | 1 to 10 | no | yes | N/A |
| 6. benzonitrile | 1 to 18 | yes | yes | 10 min |
| 7. acetonitrile | 1 to 230 | no | yes | N/A |
| 8. caffeine | 1 to 100 | yes | N/A | 30 s |
| 9. thebaine | 1 to 93 | yes | N/A | 1 min |
| 10. trimethylacetic acid | 1 to 2 | yes | no | 30 s |
| 11. 10-undecenoic acid | 1 to 10 | yes | yes | 2 min |
| 12. ethyl acetate | 1 to 2 | yes | no | 30 s |
| 13. cyclohexanecarboxaldehyde | 1 to 4 | yes | no | 30 s |
| 14. benzene | 3 to 1 | yes | no | 15 s |
| 15. methanol | 10 to 1 | yes | N/A | 1 min |

^a Moles of template to moles of monomer 1.

groups' high absorbency at 271 nm, which is near the photoinitiator λ_{max} of 247 nm. Pyridine and 3,5-dimethylpyrazole both absorb in the far-UV range (λ_{max} 260 nm and approximately 214 nm), but more importantly the basicity of the nitrogen allowed abstraction of the proton from the protonated epoxide, preventing chain elongation. The IR signature of dimethylformamide was too small to be seen when mixed with the monomer in a 1:100 DMF/monomer ratio, but polymerization occurred after 2 min. When the DMF/monomer ratio was changed to 1:10, the dimethylformamide carbonyl peak at 1680 cm^{-1} and C–N bond peak at 1385 cm^{-1} were large and sharp. After 2 min of exposure to the UV light, these two peaks had vanished and only a small amount of polymer had formed. Potentially, the dimethylformamide carbonyl oxygen may have nucleophilically attacked the activated epoxide and formed a permanent covalent bond to the polymer, quenching any further growth by that particular chain. This hypothesis was substantiated by the similar behavior exhibited by nitrile moieties. In fact, polymerization was found to be greatly hindered by the presence of any nitrile group. The sharp CN triple bond stretching peak at 2275 cm^{-1} in acetonitrile and 2280 cm^{-1} for benzonitrile underwent drastic reductions in intensity and broad peaks characteristic of C=N double bonds appeared at 1660 and 1670 cm^{-1} (MeCN and $\text{C}_6\text{H}_5\text{CN}$, respectively). These data suggest that strongly nucleophilic nitrogens were able to attack the acid-activated epoxides and covalently terminate the chain. Weaker nucleophiles such as the carbonyl oxygen of ethyl acetate and cyclohexanecarboxaldehyde showed no sign of reacting with the monomer during the polymerization step.

When trimethylacetic acid was combined with the monomer/photoinitiator mixture unexpected minor shoulder peak appeared at 1735 cm^{-1} on the carboxylic acid carbonyl peak (1700 cm^{-1}) before any exposure to UV light. Also, no broad peak was found in the hydroxyl region of the spectrum. Fifteen seconds of UV light brought about complete polymerization; however, no change occurred in the IR spectrum. The minor shoulder peak still remained on the carboxylic acid carbonyl peak and no C–O stretch was present. A second monomer/photoinitiator/trimethylacetic acid solution was created and then washed with a NaOH solution to

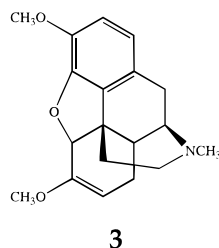
(5) Crivello, J.; Lee, J. *J. Polym. Sci.: Part A: Polym. Chem.* **1989**, *27*, 3951.

extract the carboxylic acid. The base solution was acidified to pH 4 with H_2SO_4 and then extracted with diethyl ether to recover the trimethylacetic acid. The IR spectrum of this acid showed no ester peak, though a weak, broad C–O stretch peak was observed. These results suggest that the highly polar trimethylacetic acid forms a hydrogen-bonded dimer in the very non-polar monomer/photoinitiator solution. By dimerizing, the carboxylic acid groups were buried in a shell of methyl groups which protected the acids from becoming incorporated into the polymer matrix. Next, 10-decenoic acid was dissolved in a monomer/photoinitiator mixture, and an IR spectrum was recorded. There was no sign of the hydrogen bonded carboxylic acid peak around 1735 cm^{-1} ; however, a very large, broad C–O stretch peak and an intense C=O carboxylic acid peak were present. After polymerization of this sample, the carboxylic acid carbonyl peak had been completely replaced by an ester carbonyl peak, and the C–O stretch peak was reduced in intensity. The long-chain hydrocarbon structure of 10-decenoic acid may have allowed it to dissolve individually into the monomer/photoinitiator solution rather than dissolving as hydrogen-bonded dimers. The exposed acid groups were then open to electrophilic attacks during polymerization.

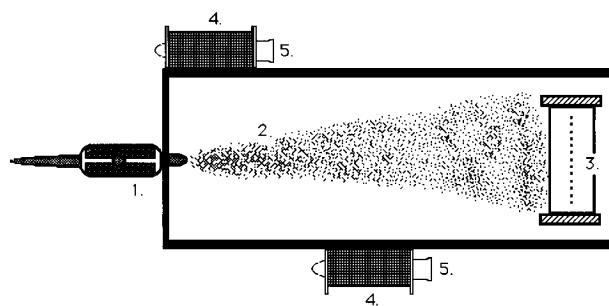
The multifunctional caffeine and thebaine templates did not hinder the polymerization step. Neither of these molecules were highly soluble in the monomer/photoinitiator solution, which made obtaining their IR spectra impossible.

Polymerization was not hindered by the presence of the aromatic ring of benzene or the hydroxyl functional group of methanol. Whereas polymerization with a small excess of benzene gave a hard polymer, the large excess of methanol resulted in a very soft, gelatinous matrix. Removal of the methanol by vacuum caused the gel-like polymer to shrink and harden. Polymerization of the solvated monomers suggests that the synthesis of porous polymer matrices may be possible.

Templating Polymeric Microbeads. To generate specifically imprinted microbeads, the polymerization was done in the presence template of the non-hydroxylic morphine derivative thebaine (3). Thebaine is a large,

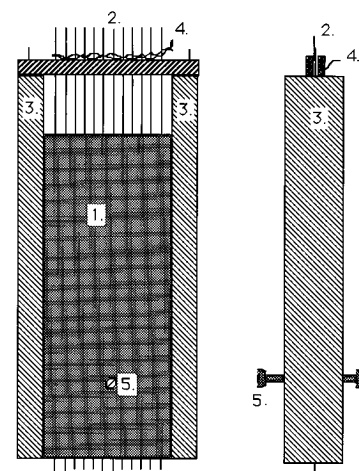


rigid molecule containing a variety of functionalities which should result in the formation of a shape-specific cavities. In a sample run, 37.8 mg of thebaine was dissolved in 4.4 g of monomer along with the 2.5 mol % of the photoinitiator. This mixture was sprayed through the reaction chamber (Figure 1) which was flooded with UV light from two 400 W medium-pressure Hanovia Hg lamps. The microdrops of the aerosol mist polymerized as they passed through the reaction chamber.⁶ An electrostatic precipitator (Figure 2) was used to collect



1. Badger Airbrush Model 150 IL and Trigger Clamp
2. Aerosol Mist of Monomer, Template, and Photoinitiator
3. Electrostatic Precipitator (see Fig. 2)
4. Curved Aluminum Mirrors
5. 400 W Hanovia Medium Pressure UV Lamps & Quartz Cooling Jackets

Figure 1. Reaction chamber.



1. Collection Electrode (stainless steel plate, 24.25" x 7")
2. Discharge Electrodes (steel wire, 28" long, 0.062" diameter)
3. Electrode Support Structures (wood, 24" x 2.5" x 1")
4. Discharge Electrode Power Lead
5. Collection Electrode Power Leads

The power source for the electrostatic precipitator puts out 13.5 kV DC at 0.13mA.

Figure 2. Electrostatic precipitator.

the microbeads on grounded plates. The microbeads were removed from the electrostatic precipitator with yields ranging from 24% to 33% of well-formed beads as a free-flowing off-white powder. The remaining 70% of the sprayed material was found deposited as a film on the walls of the reaction chamber. It is thought that the reaction chamber design could be improved to optimize microbead yield. Soxhlet extraction of the thebaine-imprinted beads removed $9.0\ \mu\text{mol}$ of thebaine/g of bead, approximately 32% of the total thebaine present. The molecular recognition properties of the beads were tested by stationary phase analysis. Samples of thebaine-templated beads and nontemplated beads were shaken overnight while soaking in 10 mL of a 2.0 mM thebaine 95/5 (v/v) acetonitrile–acetic acid solution.⁷ The following day the beads were collected by vacuum filtration and allowed to air dry. The two bead samples were then washed with 25 mL of methanol to extract thebaine captured by the beads. The methanol was removed and the remaining residues were trans-

(6) Crivello, J.; Hobbs, private communication with J. Crivello.

(7) Andersson, L.; Muller, R.; Vlatakis, G.; Mosbach, K. *Proc. Natl. Acad. Sci. U.S.A.* **1995**, *92*, 4788.

Table 2. Concentrations of Thebaine Retained by Thebaine-Templated Beads and by Nontemplated (Blank) Beads

| bead sample | mass of beads | thebaine retained | thebaine/beads ^c | T/B ratio ^d |
|--|---------------|-------------------|-----------------------------|------------------------|
| blank ^a | 44.74 mg | 78 μ g | 2 μ g/mg | |
| templated ^a | 46.74 mg | 187 μ g | 4 μ g/mg | 2.0 |
| blank ^d | 47.68 mg | 143 μ g | 3 μ g/mg | |
| templated ^b | 45.64 mg | 574 μ g | 13 μ g/mg | 4.3 |
| blank ^b | 45.34 mg | 190 μ g | 4 μ g/mg | |
| templated ^b | 46.12 mg | 380 μ g | 8 μ g/mg | 2.0 |
| blank ^b | 48.90 mg | 287 μ g | 6 μ g/mg | |
| templated ^b | 49.25 mg | 623 μ g | 13 μ g/mg | 2.2 |
| Combination of the T/B ratio for these 4 runs: | | | average: | 2.6 |
| | | | standard deviation: | 1.1 |

^a Shaken in a 2.0 mM thebaine 98/2 (v/v) hexane–acetic acid solution for 24 h. ^b Shaken in a 2.0 mM thebaine 95/5 (v/v) acetonitrile–acetic acid solution for 24 h. ^c Amount of thebaine retained/mg of bead material. ^d Ratio of thebaine retained by thebaine-templated beads with respect to blank bead thebaine retention.

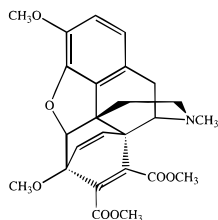
Table 3. Concentrations of 4 Retained by Thebaine-Templated Beads and by Nontemplated (Blank) Beads

| bead sample ^{a,b} | mass of beads ^c (mg) | modified thebaine (4) retained ^d (μ g) | modified thebaine (4)/beads | T/B ratio ^e |
|--|---------------------------------|--|-----------------------------|------------------------|
| blank | 46.76 | 230 | 4.9 (μ g/mg) | |
| templated | 46.53 | 246 | 5.3 | 1.1 |
| blank | 46.56 | 215 | 4.6 | |
| templated | 46.68 | 390 | 8.5 | 1.8 |
| blank | 41.30 | 129 | 3.1 | |
| templated | 42.70 | 238 | 5.6 | 1.8 |
| blank | 46.50 | 468 | 10.1 | |
| templated | 40.50 | 285 | 7.0 | 0.7 |
| blank | 31.78 | 222 | 7.0 | |
| templated | 38.79 | 316 | 8.1 | 1.2 |
| blank | 44.64 | 468 | 10.5 | |
| templated | 38.79 | 390 | 10.0 | 1.0 |
| combination of the T/B ratio for these 4 runs: | | | average: | 1.3 |
| | | | standard deviation: | 0.5 |

^a Shaken in a 2.0 mM 4 95/5 (v/v) acetonitrile–acetic acid solution. ^b Same thebaine-templated beads as used in Table 2. ^c Amount of 4 retained in sample of bead material. ^d Amount of 4 retained/mg of bead material. ^e Ratio of 4 retained by thebaine-templated beads with respect to blank bead 4 retention.

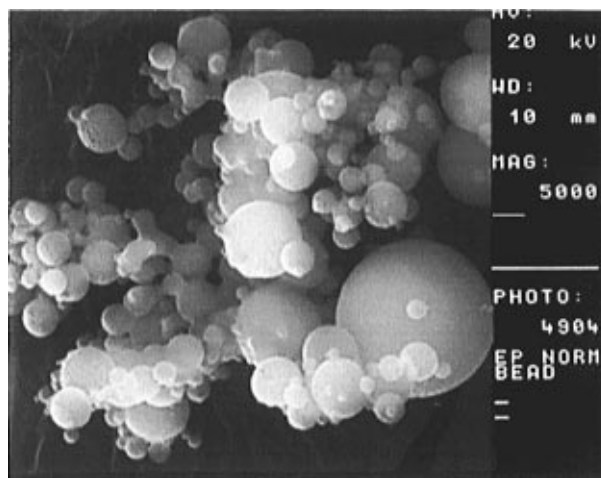
ferred to NMR tubes. Thebaine concentrations were measured using toluene as an internal standard. These values are reported in Table 2. Nonspecific thebaine adhesion by the blank beads' surfaces during the acetonitrile/acetic acid/thebaine solution removal accounted for the retention amounts shown by the non-imprinted beads. Soxhlet extraction of washed beads removed no measurable amounts of thebaine.

There was concern over whether the selectivity of the imprinted beads for thebaine was due to the existence of thebaine-specific cavities or to an increased, nonselective porosity of these beads resulting from the presence of thebaine during polymerization. To test this, thebaine-imprinted and nonimprinted beads were shaken overnight in 2.0 mM 4 in 95/5 (v/v) acetonitrile–acetic acid. In contrast to the results in Table 2, upon removal of 4 from the beads it was found to have been bound to both bead types in similar quantities. These values are reported in Table 3.



4

Examination of the microbeads by scanning electron microscopy (SEM) revealed regularly shaped spheres of

**Figure 3.** SEM photograph of polymeric microbeads.

varying size along with some joined or fused sphere structures (Figure 3). Size determinations by laser light scattering indicated that the microbeads ranged in size from 10 to 70 μ m in diameter, with 50% of the sample near 31 μ m. Studies in other labs have shown this polymer to be quite hard⁴ and resistant to swelling in most organic solvents with the exception of ethyl acetate and methylene chloride.

Conclusions

This new method of microbead production occurs directly, without the long irradiation times, organic

solvents, or grinding required by traditional production of templated polymer. Preliminary results have shown that thebaine-imprinted beads retained $\sim 2\text{--}4.3$ times as much of this template compared to nonimprinted beads. These sites are thebaine specific. The rebinding site population of thebaine-templated beads was $\sim 1.3\text{--}4.1$ $\mu\text{mol/g}$ of beads. This is slightly higher than Mosbach's morphine-templated polymer, which was reported to have site populations between 1.2 and 3.4 $\mu\text{mol/g}$.⁷ As mentioned earlier, 9.0 μmol of thebaine are extracted from 1 g of imprinted beads. Therefore, we show rebinding values of 14–46%, which are considerably higher than the 10–15% rebinding capabilities found in other templated polymers using noncovalent forces for molecular recognition.⁸ Under normal conditions, a variety of moieties can be present during cationic polymerization for microbead formation. Primary amines and nitriles must be avoided, but olefins, hindered carbonyls, and nitro groups pose little problem. This knowledge will allow the creation of monomers modified to offer stronger electronic interactions with the template molecules. The dimerization of carboxylic acid bearing polar molecules in the highly nonpolar monomer suggest that dimerization of a template molecule's carboxylic acid with that of a small, epoxide-containing molecule will bring about strategically placed hydrogen-bonding sites in the cavities of the polymer. Modifications of template molecules by replacing incompatible groups with isosteric and isoelectronic ones can also be pursued. For instance, acyl fluoride may prove to be a useful model for carboxylic acid groups.

This material has a number of potential uses. It could be used as a highly specific stationary phase for chromatography, where the molecular selectivity was controlled by the choice of template molecule. More importantly, pseudoenzymatic abilities may be created by using transition-state analogues as templates. This technique has been used for years in the area of catalytic antibodies⁹ and more recently by researchers using imprinted polymers.¹⁰ The rebinding capabilities of our microbeads should make them ideal structures for performing acts of catalysis.

Experimental Section

General Methods. Proton and carbon-13 NMR spectra were recorded on a Varian Unity-500 spectrometer. Infrared spectra (IR) were recorded on a Perkin-Elmer 298 IR spectrophotometer. Band frequencies are reported in cm^{-1} . Laser light-scattering size determinations were done with a Malvern Instruments EASY particle Sizer M3.0.

Functional Group Tests. The effect of assorted functional groups on the rate of polymerization was tested in the following general method. A monomer/(0.5% mol) photoinitiator mixture (10 mg) was combined with 7 μL of test molecule on a salt plate. A second salt plate was placed over the mixture, and the IR spectrum was recorded. The salt plates were then exposed to UV light from a single medium-pressure Hanovia 400 W Hg lamp for 10 s to 10 min, depending on how long the polymerization step required. Polymerization was considered complete when the two plates became stuck together.

Thebaine-Imprinted Microbeads. Thebaine (16.7 mg, 0.05 mmol), photoinitiator (90.3 mg, 0.14 mmol), and monomer (2.1857 g, 5.70 mmol) were combined in the fluid reservoir of a Badger 150 IL air brush. The solution was sonicated for 10 min to ensure complete mixing. The reservoir was attached to the air brush whose trigger was locked into the "thick, slow" painting mode. After attaching the air-brush assembly to the reaction chamber and turning on the two medium-pressure Hg UV lamps, spraying of the thebaine/monomer/photoinitiator mixture was started by turning on the air flow to the air brush. The air flow was kept at a pressure of 20 psi. After spraying was completed the air flow to the air brush was stopped, the lamps were shut off and the electrostatic precipitator was detached from the reaction chamber. The microbeads (825.4 mg, 36% yield) were removed from the collection plates and discharge electrodes using a rubber spatula. Elimination of thebaine from the microbeads was accomplished by three 24 h Soxhlet extractions with methanol.

Thebaine Bead Retention. Thebaine-templated beads (48.68 mg) and nontemplated beads (48.58 mg) were shaken for 24 h at room temperature in 10 mL solutions of a 2.0 mM thebaine–95/5 (vol/vol) acetonitrile:anhydrous acetic acid. The beads were then collected by vacuum filtration and allowed to air-dry for 8 h. Thebaine was extracted with five 5 mL methanol washes where the beads were stirred with the methanol for 5 min and then collected on a fritted glass funnel via vacuum filtration. The washes were collected in two 50 mL round-bottom flasks. The methanol was removed from the two samples by rotary evaporation leaving behind off-white residues. These residues were then dissolved in small amounts of methanol and transferred to 5 mL flasks. The methanol was again removed. The residues were then dissolved by twice adding 300 μL of a 6.3 mM toluene in chloroform-*d* solution to the flasks and pipetting the resulting mixtures to NMR tubes. The peaks used for comparison were thebaine's cyclohexadiene methoxy-group protons at 3.60 ppm, its aromatic methoxy protons at 3.85 ppm, and the toluene's methyl peak at 2.36 ppm.

17,18-Bis(methoxycarbonyl)-6,14-ethenocodeine Methyl Ether (4). This compound was prepared by the method of Rapoport and Sheldrick.¹¹ A solution of 391.6 mg (1.26 mmol) of thebaine (3) and 183.9 mg (1.29 mmol) of dimethyl acetylenedicarboxylate in 5 mL of dry benzene was stirred at 50 °C for 1 h. The yellowish solution was allowed to stand overnight at room temperature. The desired product precipitated out as off-white crystals, mp 136–139 °C. Purification was accomplished by dissolving the crystals in benzene (room temperature) and washing the solution with a 0.3 M phosphate, pH 3.0 solution, followed by evaporation of the benzene in vacuo at 25 °C until crystallization began. Colorless crystals formed, mp 141–142 °C, ¹H NMR (500 MHz, chloroform-*d*) δ 1.59 (s, 2 H), 2.30 (s, 3 H), 2.51 (m), 3.21 3.25 (d, *J* = 18.6 Hz, 1 H), 3.58 (d, *J* = 0.5 Hz, 3 H), 3.75 (s, 3 H), 3.85 (d, *J* = 11.7 Hz, 3 H), 3.88 (d, *J* = 6.8 Hz, 1 H), 4.73 (s, 1 H), 5.53 (d, *J* = 7.9 Hz, 1 H), 6.23 (m, 1 H), 6.60 (dd, *J* = 48.1, *J* = 8.3, 1 H). ¹³C NMR (125 MHz, chloroform-*d*) δ 26.08, 38.59, 46.30, 48.02, 55.22, 55.60, 56.09, 56.25, 58.46, 59.37, 59.99, 90.41, 98.67, 117.37, 123.33, 130.38, 131.60, 132.91, 136.15, 138.89, 142.28, 145.59, 148.12 152.67, 168.81, 169.05. IR (neat, NaCl) 2937.8, 1725.5, 1626.6, 1582.7 1500.3 1443.9, 1273.8 cm^{-1} .

Bead Retention of 3. Thebaine-templated beads (48.68 mg) and nontemplated beads (48.58 mg) were shaken for 24 h at room temperature in 10 mL solutions of a 2.0 mM 17,18-bis(methoxycarbonyl)-6,14-ethenocodiene methyl ether 95/5 (vol/vol) acetonitrile:anhydrous acetic acid solution. The beads were then collected by vacuum filtration and allowed to air-dry for 8 h. 4 was extracted with five 5 mL methanol washes where the beads were stirred in the fritted glass funnel with the methanol for 5 min and then collected via vacuum filtration. The two sets of washes were collected in two 50 mL round-bottom flasks. The methanol was removed from the two samples by rotary evaporation, leaving behind off-white

(8) Sellergren, B.; Shea, K. *J. Chromatogr.* **1993**, 635, 31.

(9) (a) Tramontano, A.; Janda, K. D.; Lerner, R. *Science* **1986**, 234, 1566. (b) Pollack, S.; Jacobs, J.; Schultz, P. *Science* **1986**, 234.

(10) Wulff, G. *Angew. Chem., Int. Ed. Engl.*, **1995**, 34, 1812.

(11) Rapoport, H.; Sheldrick, P. *J. Am. Chem. Soc.* **1963**, 85, 1636.

residues. These residues were then dissolved in small amounts of methanol and transferred to 5 mL flasks. The methanol was again removed. The residues were then dissolved by twice adding 300 μ L of a 6.3 mM toluene (internal standard) in chloroform-*d* solution to the flasks and pipetting the resulting mixtures to NMR tubes. The peaks of interest were 4's ester methoxy protons at 3.75 and 3.80 ppm, cyclohexadiene methoxy-group protons at 3.60 ppm, its aromatic methoxy

proton peak at 3.85 ppm, and the toluene's methyl peak at 2.36 ppm.

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