

freezer for 3 h. The product was collected by filtration, washed with cold ethanol, and dried in vacuo to yield **9** (33 g, 93%): mp 144–145 °C;  $^1\text{H NMR}$   $\delta$  0.83 (6 H, t,  $\text{CH}_2\text{CH}_2\text{CH}_3$ ), 1.19 (6 H, t,  $\text{CO}_2\text{CH}_2\text{CH}_3$ ), 1.35 (4 H, m,  $\text{CH}_2\text{CH}_2\text{CH}_3$ ), 2.20 (6 H, s,  $\text{CH}_3$ ), 2.29 (4 H, t,  $\text{CH}_2\text{CH}_2\text{CH}_3$ ), 3.82 (2 H, s, pyrrole- $2\text{-CH}_2$ ), 4.18 (4 H, q,  $\text{CO}_2\text{CH}_2\text{CH}_3$ ), 9.32 (2 H, br, NH); high-resolution MS,  $M^+$  402.25245 (calcd for  $\text{C}_{23}\text{H}_{34}\text{N}_2\text{O}_4$  402.25184).

**Bis(4-ethyl-3-propyl-2-pyrrolyl)methane (10).** The above bis(pyrrolyl)methane diester (40 g, 0.099 mol), 95% ethanol (140 mL), and 1 N aqueous sodium hydroxide (40 mL) were mixed in a 500-mL round-bottom flask and heated at reflux for 2 h. The condenser was then removed and the clear yellow solution concentrated to half its original volume by boiling. Water (100 mL) was added, and the solution was concentrated until its boiling point reached a minimum of 100 °C. The condenser was then replaced and heating continued for 12 h. The contents were then poured while hot into a 250-mL beaker and allowed to cool in the refrigerator. The oil-like product which solidified over the course of 2 days was collected, washed with water, and dried. This air- and light-sensitive compound was generally used without further purification. For analysis, samples were purified by chromatography on silica gel (dichloromethane eluent):  $^1\text{H NMR}$   $\delta$  0.95 (6 H, t,  $\text{CH}_2\text{CH}_2\text{CH}_3$ ), 1.53 (4 H, m,  $\text{CH}_2\text{CH}_2\text{CH}_3$ ), 2.05 (6 H, s,  $\text{CH}_3$ ), 2.41 (4 H, t,  $\text{CH}_2\text{CH}_2\text{CH}_3$ ), 3.79 (2 H, s, pyrrole- $2\text{-CH}_2$ ), 6.3 (2 H, s, pyrrole H-5); MS,  $m/e$  (relative intensity) 258 (52), 215 (21), 197 (17), 136 (100).

**Bis(5-formyl-4-methyl-3-propyl-2-pyrrolyl)methane (11).** The  $\alpha$ -free bis(pyrrolyl)methane **10** (5 g, 0.0194 mol) was dissolved in freshly distilled DMF (25 mL) and cooled to 0 °C, and  $\text{POCl}_3$  (6 mL, 0.066 mol) was added dropwise to the stirred solution. The temperature was maintained below 5 °C. After the addition was complete, the mixture was stirred for 2 h at room temperature. The gray precipitate was collected and washed with DMF. The solid was then dissolved in water (50 mL) and made basic with 7.5 N sodium hydroxide solution. An oil separated off, which gradually solidified. This brown solid was collected by filtration, washed with water, and dried in vacuo to yield 4.0 g (66%) of **11**. Further purification to yield a yellow powder was effected by multiple recrystallizations from chloroform-hexane: mp 195–196 °C;  $^1\text{H NMR}$   $\delta$  0.86 (6 H, t,  $\text{CH}_2\text{CH}_2\text{CH}_3$ ), 1.39 (4 H, m,  $\text{CH}_2\text{CH}_2\text{CH}_3$ ), 2.20 (6 H, s,  $\text{CH}_3$ ), 2.35 (4 H, t,  $\text{CH}_2\text{CH}_2\text{CH}_3$ ), 3.90 (2 H, s, pyrrole- $2\text{-CH}_2$ ), 9.48 (2 H, s, CHO), 11.00 (2 H, br, NH); MS,  $m/e$  314 (43), 285 (36), 271 (10), 163 (100).

**1,3-Bis[5-(2,8-diethyl-3,7,12,18-tetramethyl-13,17-dipropyl)porphyrinyl]benzene (1).** This compound was prepared by several different procedures.

**Procedure I.** The bis(pyrrolyl)methane **6** (200 mg, 0.375 mmol) and the bis(formylpyrrolyl)methane **11** (235 mg, 0.75 mmol) were dissolved in 70 mL of MeOH or in 70 mL of MeOH/THF (1:1 v/v), and the reaction vessel was flushed with nitrogen. The acid catalyst,  $\text{HClO}_4$  (0.5 mL) or *p*-toluenesulfonic acid (0.5 g), was then added and the reaction left to stir for 24 h in the dark. Sodium acetate (0.5 g) in MeOH was then added followed by a solution of *o*-chloranil in MeOH (0.55 g, 2.25 mmol). After being stirred in the dark for several hours, the reaction mixture was poured into water (300 mL) and extracted with 100-mL portions of chloroform until the extracts were pale in color. After the mixture was dried over  $\text{MgSO}_4$  and filtered, a saturated solution of zinc acetate in MeOH (20 mL) was added to the organic layer and the whole heated at reflux for 20 min. After cooling, the solution was washed with water (3  $\times$  100 mL) and dried over  $\text{MgSO}_4$ . After being taken to dryness on the rotary evaporator, the biszinc complex of **1** was purified from undesired byproducts by filtration through a plug of silica gel (dichloromethane eluent). Demetalation was effected by stirring for 8 h in 7 mL of a mixture of trifluoroacetic acid, concentrated HCl, and water (2:2:1 by volume). After neutralization with an aqueous bicarbonate solution, the free base porphyrin was extracted into dichloromethane, dried over  $\text{MgSO}_4$ , and taken to dryness in vacuo to yield between 38 and 45 mg of **1** (9–11% yield). This product was one clean spot on TLC (silica gel/3% MeOH in chloroform). Material for analysis could, however, be obtained by chromatography on silica gel (1% MeOH in  $\text{CH}_2\text{Cl}_2$  eluent) followed by recrystallization from dichloromethane-hexane.

**Procedure II.** The precursors **6** (106 mg, 0.20 mmol) and **11** (125 mg, 0.40 mmol) were dissolved in HOAc (50 mL), and HI

(3 mL) was added. After the flask was flushed with nitrogen, the reaction was allowed to stir for 24 h in the dark. The red slurry was poured into an excess of aqueous potassium carbonate. After reaction was extracted into dichloromethane, dried over  $\text{MgSO}_4$ , and taken to dryness, 50 mL of MeOH-THF (1:1 v/v) was added. The oxidation and purification steps were then effected as outlined above to yield 17 mg of **1** (8%).

**Procedure III.** This was carried out exactly as above only the tetraacid **5** (141 mg, 0.20 mmol) was used as a precursor instead of **6**. The yield of **1** was 14 mg (5%).  $^1\text{H NMR}$   $\delta$  -3.0 (4 H, br, pyrrole NH), 1.22 (12 H, t,  $\text{CH}_2\text{CH}_2\text{CH}_3$ ), 1.72 (12 H, t,  $\text{CH}_2\text{CH}_2\text{CH}_3$ ), 2.25 (8 H, m,  $\text{CH}_2\text{CH}_2\text{CH}_3$ ), 3.07 (12 H, s,  $\text{CH}_3$ ), 3.55 (12 H, s,  $\text{CH}_3$ ), 3.99 (16 H, m, porphyrin  $\text{CH}_2\text{CH}_2$ ), 7.82 (1 H, s, phenyl H-2), 8.27 (1 H, t, phenyl H-5), 8.90 (2 H, d, phenyl H-4 and -6), 9.78 (2 H, s, meso H-15), 10.04 (4 H, s, meso H-10 and -20);  $^{13}\text{C NMR}$   $\delta$  11.8, 14.5, 17.2, 20.2, 26.1, 28.3, 34.1, 96.0, 96.4, 118.0, 125.6, 127.6, 133.8, 135.3, 136.2, 140.0, 141.0, 141.9, 143.7, 144.8, 145.2, 146.1; UV-vis  $\lambda_{\text{max}}$  627, 576, 540, 507, 410 nm. Anal. Calcd for  $\text{C}_{74}\text{H}_{86}\text{N}_8$ : C, 81.68; H, 7.97; N, 10.30. Found: C, 81.68; H, 8.11; N, 10.08.  $\text{Zn}_2$ : UV-vis  $\lambda_{\text{max}}$  574, 541, 421, 405 nm; FAB MS (glycerol-oxalic acid matrix) shows a cluster of peaks at 1087–1091 amu (calcd for  $\text{C}_{74}\text{H}_{86}\text{N}_8\text{H}^+$ : 1087).

**Note Added in Proof.** In acting as a reviewer for this paper, Professor C. K. Chang indicated that an analogue of **1**, 1,3-bis-[5-(2,8,13,17-tetraethyl-3,7,12,18-tetramethyl)porphyrinyl]benzene, has been independently prepared in his laboratory;<sup>19</sup> he requested that this be noted.

**Acknowledgment.** This work was supported by the Robert A. Welch Foundation (Grant AP-868 to J.L.S.). J.L.S. is a recipient of a Camille and Henry Dreyfus Grant for Newly Appointed Faculty, 1984. We thank Jeffery Patterson and Maria Gou for their assistance with the synthesis of pyrroles **2**, **7**, and **8**.

**Registry No.** **1**, 102613-57-0; **1-2Zn**, 102538-52-3; **2**, 4949-58-0; **3**, 626-19-7; **4**, 102586-94-7; **5**, 102613-58-1; **6**, 102586-95-8; **7**, 4758-64-9; **8**, 102586-96-9; **9**, 102586-97-0; **10**, 102586-98-1; **11**, 102586-99-2.

(19) Chang, C. K.; Abdalmuhdi, I., unpublished work.

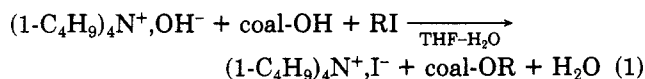
## An Investigation of the O- and C-Alkylation of Coal

M. Ettinger, R. Nardin, S. Ray Mahasay, and L. M. Stock\*

Department of Chemistry, The University of Chicago,  
Chicago, Illinois 60637

Received February 26, 1986

Liotta and co-workers developed a method for the selective O-alkylation of bituminous coal under mild conditions.<sup>1</sup> This valuable procedure, which has been used for the synthesis of a variety of modified coals,<sup>1,2</sup> employs tetrabutylammonium hydroxide as the basic catalyst and methyl iodide or another alkyl halide as the alkylation agent (eq 1). In recent applications of the method, it



became apparent that trace amounts of tetrabutylammonium ions were tenaciously retained in the alkylated coals. The presence of this material complicates the interpretation of  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra of extracts and of the products obtained in conversion reactions. In ad-

(1) Liotta, R. *J. Am. Chem. Soc.* 1981, 103, 1735.

(2) Rose, G. R.; Zabransky, R. F.; Stock, L. M.; Huang, C.; Srinivas, V. R.; Tse, K. W. *Fuel* 1984, 63, 1339.

dition, the reactions of certain alkyl halides such as 2-phenylethyl bromide provided unacceptably high yields of styrene under these conditions. Accordingly, we investigated alternate tactics for the preparation of alkylated coals.

**O-Alkylation. The Alkylation Reagent.** Several considerations suggested that alkyl tosylates might be more suitable reagents than alkyl halides. For example, the O-alkylation of 2-methylphenol with 2-phenylethyl iodide in the presence of tetrabutylammonium hydroxide yields about 55% styrene and only 45% 2-methylphenyl 2-phenylethyl ether. When the more nucleofugal 2-phenylethyl tosylate is used under the same conditions, the reaction yields only 10% styrene and 90% of the desired ether. Clearly, considerably less of the sulfonate ester is consumed in undesirable side reactions.

The O-alkylation of coal with methyl tosylate was studied first. An appropriate workup procedure was developed to ensure complete removal of any residual methyl tosylate and the tosylate salts formed in the reaction. Their removal was monitored by testing washings of the alkylated coal with barium chloride solutions and by recording the  $^1\text{H}$  NMR spectra of concentrated solutions of organic extracts of sonicated alkylated coal samples. The removal of the sulfur compounds was verified by elemental analysis which indicated that the alkylated coal had less sulfur than the original coal.

The infrared spectra of the O-methylated coals that were obtained from the reactions with methyl tosylate and methyl iodide are essentially identical. Elemental analyses establish that the H/C ratio of the methylated coal is 0.92 (compared to 0.85 for untreated coal). This value is in good agreement with the results obtained by Liotta and co-workers<sup>3</sup> and is compatible with the introduction of 5 alkyl groups per 100 carbon atoms. These results indicate that the tosylates can be used as alkylating agents and that their use does not result in contamination of the coal with sulfur compounds.

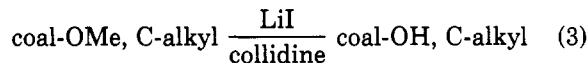
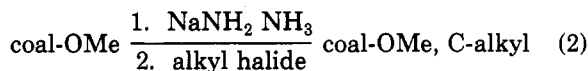
The *O*-[2-phenylethyl] and *O*-2-[(4-propylphenyl)ethyl] coals were conveniently prepared by using the corresponding tosylates.

**O-Alkylation. The Base Catalyst.** To circumvent the difficulties associated with tetrabutylammonium hydroxide, we studied the O-alkylation of coal with potassium and sodium hydroxide in moist tetrahydrofuran. The infrared spectra of the O-methylated coals prepared by using these catalysts established that the reaction was successful. The inorganic bases were easily removed with water.

The utility of the reaction with potassium hydroxide was tested by the preparation of an *O*-benzyl coal by using benzyl bromide as the alkylation reagent. The properties of the benzylated coal prepared in this way were essentially identical with the properties of the benzylated coal prepared by using tetrabutylammonium hydroxide in a previous study.<sup>2</sup> For example, the infrared spectrum of the material prepared by using potassium hydroxide exhibits the very characteristic C-H out-of-plane deformation frequencies near 700–740  $\text{cm}^{-1}$  that are indicative of O-benzylation.

While our studies of these alkylated coals are not yet complete, it is pertinent to note that the use of the inorganic bases in reactions with methyl- $^{13}\text{C}$  iodide have enabled the direct study of the upfield regions of the  $^{13}\text{C}$  NMR spectra of reaction mixtures and pyrolysis products free from the interfering resonances of the carbon atoms of tetrabutylammonium ion.

**C-Methylation.** C-Methylated coal can be prepared by treating O-methylated coal with sodium amide and methyl iodide followed by demethylation using lithium iodide in collidine (eq 2 and 3). The selectivity of C-alkylation



depends on the effective blocking of the oxygen sites. Experience suggests that two O-methylation reactions with excess base and methyl iodide are required for the preparation of a fully O-alkylated product. Elemental analysis indicates that about 7.5 methyl groups are introduced per 100 carbon atoms in these doubly O-methylated coals.

To gauge the course of the C-methylation, we compared the  $^2\text{H}$  NMR spectra of pyridine extracts of the C-methylation products from reactions using methyl- $d_3$  iodide as the alkylating agent on singly and doubly O-methylated coals. There are intense resonances at 3.5 ppm in the spectra of *O*-methyl C-methyl- $d_3$  coal prepared from singly O-methylated coal which disappear after treatment with lithium iodide and collidine. These resonances are due to *O*-methyl- $d_3$  groups formed during C-alkylation due to incomplete O-methylation. The spectra of *O*-methyl C-methyl- $d_3$  coal prepared from a doubly O-methylated coal sample contains no discernible resonances downfield of 3 ppm. Resonances due to methylation on carbon are present in the high field and these do not change on treatment with lithium iodide and collidine. The elemental analysis of the C-methyl coal prepared from doubly O-methylated coal indicates that 2.4 C-methyl groups are introduced per 100 carbon atoms in the coal.

### Experimental Section

A sample of Illinois No. 6 coal was obtained from Peabody No. 10 min in Pawnee, IL. Anal. of the coal: C, 67.65; H, 4.85; N, 1.16; Cl, 0.05; S, 4.23; ash, 12.38; O by difference, 9.58. Commercial anhydrous liquid ammonia (Matheson) was used without purification. Tetrahydrofuran was refluxed over potassium metal and distilled prior to use. Collidine, methyl tosylate, methyl iodide, and tetrabutylammonium hydroxide (1.54 M aqueous solution) were obtained from Aldrich Chemical Co. Benzyl bromide was distilled prior to use. 2-Phenylethyl tosylate, mp 38.5 °C (lit.<sup>4</sup> mp 37.4–38.0 °C) was prepared from the alcohol as described by Fieser and Fieser.<sup>5</sup> Methyl- $d_3$  iodide (99% isotopically pure) was supplied by Cambridge Isotope Company.

Infrared spectra were recorded on a Nicolet Model 20SX spectrophotometer. Potassium bromide pellets of the coal products (2–4 wt %) were dried at 60 °C for 24 h before recording the spectrum. Deuterium NMR spectra were recorded in pyridine contained in 5 mm tubes on a Varian Model XL-400 spectrometer. Proton NMR spectra were recorded on the University of Chicago 500-MHz spectrometer. Gas chromatographic analysis was carried out on a Perkin-Elmer gas chromatograph Model Sigma 3B fitted with a FID detector.

**Alkylation Reactions of Coal.** The O-alkylated coal samples using tetrabutylammonium hydroxide were prepared as described previously.<sup>2</sup> The coal residue from the reaction was washed on a Whatman PtFE membrane filter (pore size 1  $\mu\text{M}$ ) with 50% methanol water mixture after acidification with 2 N hydrochloric acid. The washings were tested with sodium tetraphenylboron and silver nitrate solutions for tetrabutylammonium salts and halides, respectively.

**Alkylation Using Alkali Hydroxides.** A freshly prepared solution of potassium or sodium hydroxide (1.5 M, 2.6 mL) was added to the suspension of coal (1 g) in tetrahydrofuran (25 mL)

(4) Saunders, W. H.; Edison, D. H. *J. Am. Chem. Soc.* 1960, 82, 138.

(5) Fieser, M.; Fieser, L. *Reagents for Organic Synthesis*, Wiley and Sons: New York, 1967; Vol. 1, p 1180.

(3) Liotta, R.; Rose, K.; Hippo, E. *J. Org. Chem.* 1981, 46, 277.

and the mixture was stirred under nitrogen for 1 h. A solution of alkyl halide (4.5 mmol) in tetrahydrofuran (5 mL) was added to the mixture and stirred for 48 h. During workup the mixture was acidified (pH 2) with 2 N hydrochloric acid and the tetrahydrofuran was removed on the rotovapor. The residue was transferred on to the membrane filter and washed with 50% methanol water mixture (2 × 200 mL) and water. The washings were tested for halide ions with silver nitrate solution. The coal samples were dried under vacuum (60 °C).

**Alkylation Using Tosylates.** A solution of the tosylate (4.5 mmol per gram of coal) in tetrahydrofuran was added to a suspension of coal in tetrahydrofuran containing an appropriate base (2.6 mmol per gram of coal). The reaction was carried out as already described except that the product was first washed with ether (50 mL per gram of coal) to remove the alkylation agent. When 2-phenylethyl tosylate and 2-[4-propylphenyl]ethyl tosylate were used, it was necessary to wash the product with 4 portions of ether to remove the alkylating agent. The coal residue was then washed with 50% methanol water mixtures and the washings were tested with barium chloride solution and sodium tetraphenylboron to test for the removal of sulfonates and tetrabutylammonium compounds. Anal. of the coal alkylated with methyl tosylate: C, 68.50; H, 5.25; S, 2.80; ash, 10.8.

**C-Alkylation of Coal.** The carbanions were prepared from O-methylated coal (3 g) with sodium amide (41 mmol) in liquid ammonia (150 mL) for 3 h. The alkyl halide (127 mmol) was added and the reaction mixture was stirred for an additional 6 h. The ammonia was allowed to evaporate under a slow stream of nitrogen and the residue was taken up in a mixture of tetrahydrofuran (50 mL) and water (50 mL) and neutralized using 6 N hydrochloric acid. The residue after evaporation of tetrahydrofuran was filtered and washed with 50% methanol water mixture (3-5 L) until the washings were free of halide ions. The coal sample was dried under vacuum (65 °C) and then transferred under nitrogen into a flask containing freshly distilled collidine (35 mL per gram of coal) and lithium iodide (2.1 g per gram of coal). The mixture was refluxed under nitrogen for 48 h and then collidine was distilled under vacuum. The residue was acidified (pH 4), filtered through a membrane filter, and washed with 50% methanol water until washings were free of any halide ion. Anal. of C-methylated coal: C, 69.46; H, 5.29; ash, 8.82.

### Enzyme-Catalyzed Synthesis of L-Acetylcarnitine and Citric Acid Using Acetyl Coenzyme A Recycling

Smita S. Patel, Hugh D. Conlon, and David R. Walt\*

Max Tishler Laboratory for Organic Chemistry,  
Department of Chemistry, Tufts University,  
Medford, Massachusetts 02155

Received March 14, 1986

Natural products chemists have developed extensive methodology to construct complex organic compounds. A great deal of effort has been directed at stereoselective bond formation to produce optically pure materials. Enzymes are involved in virtually every reaction occurring in the biosynthesis of natural products; however, they have been used only recently for large scale synthesis of organic compounds. Enzymes offer many advantages for synthesis; they are selective, are usually stereospecific, and operate at ambient temperature and pressure.<sup>1</sup> The most widely used enzymes are the isomerases and hydrolases.<sup>2</sup> There

(1) (a) Whitesides, G. M.; Wong, G. H. *Aldrichimica Acta* 1983, 16, 27. (b) Jones, J. B.; Sih, C. J.; Perlman, D. *Applications of Biochemical Systems in Organic Chemistry*, Part I and II; John Wiley and Sons: New York, 1976. (c) Whitesides, G. M.; Wong, C. H. *Angew. Chem., Int. Ed. Engl.* 1985, 24, 617.

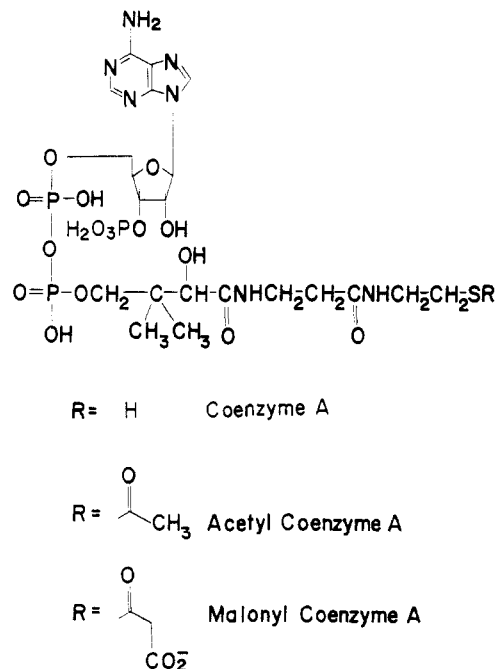


Figure 1.

is great interest in using enzymes to form carbon-carbon bonds, because complex molecules can be prepared from simpler starting materials. Very few examples of enzymatic carbon-carbon bond-forming reactions have been reported.

A large percentage of enzymes require cofactors such as XTP (X = A, C, G), NAD(P)(H), and coenzyme A (CoA). The cost of these cofactors precludes their use in large scale synthesis if stoichiometric quantities of cofactor are required. In order to make synthesis with cofactor-requiring enzymes economically feasible, the cofactors have to be regenerated and recycled in situ. Successful efforts have been made to recycle ATP<sup>3</sup> and NAD(P)(H),<sup>4</sup> but little effort has been made to recycle CoA to furnish isolable quantities of product. CoA and its derivatives (Figure 1) are the most expensive of the above cofactors (CoA - \$400 000/kg, acetyl-CoA - \$1 400 000/kg, based on Sigma catalog prices) and are useful for activating substrates toward carbon-carbon and carbon-oxygen bond formation. Acetyl-CoA is a common cellular currency for acetyl transfers and is involved in the citric acid cycle, fatty acid metabolism, glucose metabolism, and malic acid production. CoA and its derivatives are therefore indispensable for many reactions that involve stereospecific bond formation and complex molecule construction. Synthesis of organic compounds using CoA dependent enzymes will become practical only if these CoA thio esters can be recycled. We report here our successful efforts in recycling CoA and acetyl-CoA in synthesis.

As a demonstration of acetyl-CoA recycling, we chose to examine the enzyme-catalyzed aldol condensation of

(2) Selected examples include: (a) Abbot, B. J. *Adv. Biochem. Eng.* 1979, 12, 41. (b) Chibata, I.; Tosa, T.; Sato, T. *Methods Enzymol.* 1976, 44, 739. (c) Strandberg, G. W.; Smiley, K. L. *Appl. Microbiol.* 1971, 21, 588. (d) Cambou, B.; Klivanov, A. M. *J. Am. Chem. Soc.* 1984, 106, 2687. (e) Laumen, K.; Reimerdes, E. H.; Schneider, M. *Tetrahedron Lett.* 1985, 26, 407.

(3) (a) Pollak, A.; Baughn, R. L.; Whitesides, G. M. *J. Am. Chem. Soc.* 1977, 99, 2366. (b) Rios-Mercadillo, V. M.; Whitesides, G. M. *J. Am. Chem. Soc.* 1979, 101, 5828.

(4) (a) Wong, C. H.; Whitesides, G. M. *J. Am. Chem. Soc.* 1981, 103, 4890. (b) Wong, C. H.; Whitesides, G. M. *J. Org. Chem.* 1982, 47, 2816. (c) Wong, C. H.; Sweers, H. M.; Drueckhammer, D. G. *J. Am. Chem. Soc.* 1985, 107, 4028.