# Designed Catalysts. A Synthetic Network Polymer That Catalyzes the Dehydrofluorination of 4-Fluoro-4-(*p*-nitrophenyl)butan-2-one

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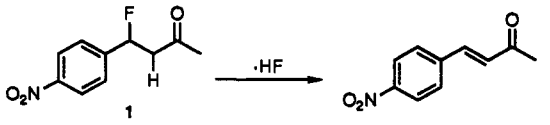
Template polymerization has been employed for the creation of binding sites at or near the surface of highly cross-linked network polymers.[1-12] The binding sites, formed during polymerization, incorporate an array of organic functional groups with a microenvironment shape and size complementary to the template (substrate) molecule. In this communication we describe an application of template polymerization for designing network polymers as catalysts.[13,14]

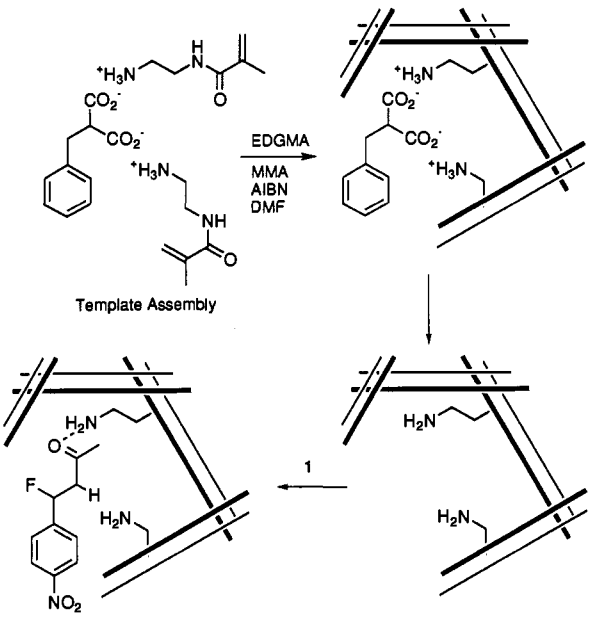
The reaction targeted is the dehydrofluorination of 4-fluoro-4-(*p*-nitrophenyl)butan-2-one (**1**), a system studied by Schultz and co-workers using the catalytic antibody approach.[15]




**1** (1)

Our goal was to develop a binding site for **1** that also positions a polymer-bound base in close proximity to the $\alpha$-hydrogen of the substrate.[16] As illustrated in Scheme I, the template molecule **2** (benzylmalonic acid) was used to orient *N*-(2-aminoethyl)-methacrylamide (**3**) monomers prior to polymerization.[17] The bulk of the polymerization solution consisted of a mixture of ethylene glycol dimethacrylate (EGDMA, 80 mol %), methyl methacrylate (MMA, 17 mol %), and **3** (3 mol %) in DMF solvent (1:1 volume ratio of monomers to solvent). The template assembly was present at 1.5 mol % of the total polymerizable monomers.

**Scheme I.** Catalyst Design for the Dehydrohalogenation of **1**




The free radical polymerization was initiated by AIBN. A control polymer of composition identical to that of templated polymer but containing randomly-oriented amino groups was made by substituting the benzylmalonic acid (**2**) with 2 equiv of acetic acid.

The resulting polymers are insoluble open-cell macroporous solids[18] with high internal surface areas (365 $m^2/g$). The template molecule **2** was removed from the polymer by washing the crushed solid with dilute aqueous NaOH. Examination of the filtrate shows 78–85% recovery of the template.[19]

A preliminary survey of the catalytic performance of the polymer was performed in benzene using a 10:1 ratio of catalytic sites to substrate **1**.[20] By monitoring of the absorbance of the suspension at 330 nm, both templated and control polymers were found to catalyze the dehydrofluorination of **1**. The rate of dehydrofluorination by the templated polymer ($k_{template}$) under pseudo-first-order conditions was 3.2 times greater than $k_{control}$ (not optimized).

Scheme I suggests that the catalytic site relies on a hydrogen-bonding interaction between polymer and substrate, and thus it was anticipated that the polarity of the reaction solvent should affect performance. Consistent with this expectation was the finding that the rate of reaction of the templated polymer with **1** slowed down in more polar solvents. The *relative* rate of reaction ($k_{template}/k_{control}$) dropped to 2.2 if the reaction was run in acetonitrile and dropped to 1.5 if the reaction was run in EtOH. This solvent effect is *opposite* to what one observes in the homogeneous reactions of **1** and to what is generally observed for E2 elimination reactions.[21]

By analogy to site-directed mutagenesis, template polymerization permits manipulation of functionality at the catalytic site by changing the template molecule. In an effort to understand the origins of catalyst performance, a series of polymers were

(1) For a review, see: Wulff, G. *Polymeric Reagents and Catalysts;* Ford, W. T., Ed.; ACS Symposium Series 308; American Chemical Society: Washington, 1986; p 186.
(2) Wulff, G.; Vietmeier, J.; Poll, H. *Makromol. Chem.* **1987**, *188*, 731.
(3) Vlatgakis, G.; Andersson, L.; Müller, R.; Mosbach, K. *Nature* **1993**, *361*, 645.
(4) Mosbach, K.; Sellergren, B.; Lepisto, M. *J. Am. Chem. Soc.* **1988**, *110*, 5853.
(5) Shea, K. J.; Dougherty, T. K. *J. Am. Chem. Soc.* **1986**, *108*, 1091.
(6) Shea, K. J.; Sasaki, D. Y. *J. Am. Chem. Soc.* **1989**, *111*, 3442.
(7) Shea, K. J.; Stoddard, G. J.; Shavelle, D. M.; Wakui, F.; Choate, R. M. *Macromolecules* **1990**, *23*, 4497.
(8) Shea, K. J.; Spivak, D. A.; Sellergren, B. *J. Am. Chem. Soc.* **1993**, *115*, 3368.
(9) Mosbach, K.; Rosatzin, T.; Andersson, L.; Simon, W. *J. Chem. Soc., Perkin Trans. 2* **1991**, 1261.
(10) Mosbach, K.; Fisher, L.; Ekberg, B. *J. Am. Chem. Soc.* **1991**, *113*, 9338.
(11) (a) Shea, K. J.; Sasaki, D. Y. *J. Am. Chem. Soc.* **1991**, *113*, 4109. (b) Shea, K. J.; Thompson, E. A. *Macromolecules* **1985**, *18*, 814.
(12) Wulff, G.; Schulze, I. *Isr. J. Chem.* **1978**, *17*, 291.
(13) Leonhardt, A.; Mosbach, K. *React. Polym., Ion Exch., Sorbents* **1987**, *6*, 285.
(14) Mosbach, K.; Robinson, D. K. *J. Chem. Soc., Chem. Commun.* **1989**, 969.
(15) Shokat, K. M.; Leumann, C. J.; Sugasawara, R.; Schultz, P. G. *Nature* **1989**, *338*, 269.
(16) Earlier efforts to elicit a catalytically active site using *N*-(*p*-nitrobenzyl)glycine ethyl ester as template was not successful. The resulting polymer bound the template but did not catalyze the dehydrofluorination of **1**.
(17) An X-ray crystal structure of bis(ethylammonium) benzylmalonate revealed the two carboxylate groups independently associated with their ethylammonium counterions. Replacing benzylmalonate with 4-fluoro-4-(*p*-nitrophenyl)butan-2-one (**1**) in a reactive conformation ($\alpha$H–$\beta$F torsion angle 180°, with both bonds coplanar to the carbonyl and phenyl $\pi$ systems) positions an amine nitrogen 3.6 Å from the $\alpha$ hydrogen of **1** and with hydrogen bonding between the second amine and substrate carbonyl.
(18) (a) Guyot, A.; Bartholin, M. *Prog. Polym. Sci.* **1982**, *8*, 277. (b) Heitz, W. *Adv. Polym. Sci.* **1977**, *23*, 1. (c) Sherrington, D. C. In *Polymer-Supported Reactions in Organic Synthesis*; Hodge, O., Sherrington, D. C., Eds.; John Wiley and Sons Ltd.: New York, 1980; Chapter 1.
(19) Subsequent washings liberate only trace amounts of template. These residual noncovalently bound molecules occupy inaccessible domains in the polymer.
(20) The number of sites was calculated on the basis of recovered benzylmalonic acid (**2**) (meg/(g of polymer)) and assumes that all sites are catalytically active.

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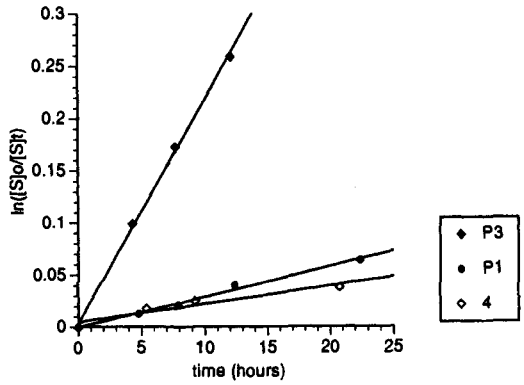



**Figure 1.** First-order plot of the dehydrofluorination of **1** under conditions of excess substrate to catalyst. A benzene solution 33 mM in **1** and 40 mM in pyridine was added to polymer to produce a ratio of polymer-bound amine to substrate of 1:17. **P3** demonstrates 7 turnovers after 12 h. ◇4 represents a homogeneous reaction using *N*-(2-aminoethyl)-acetamide (**4**) as the base.

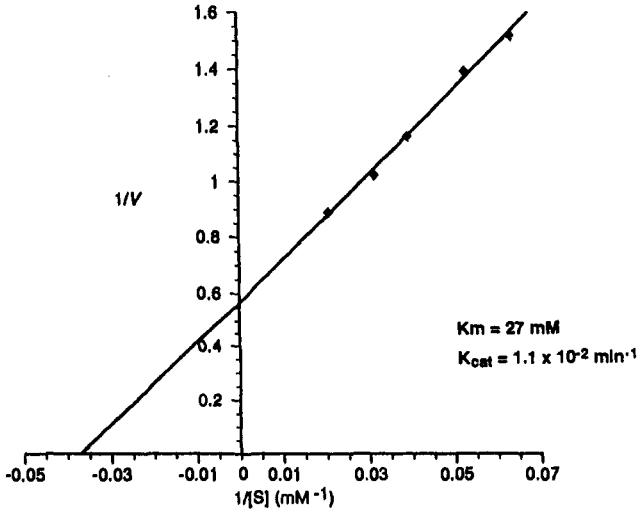
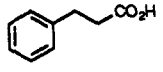
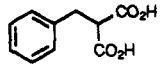
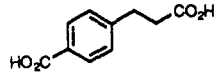
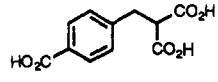



**Figure 2.** Lineweaver–Burk plot of the dehydrofluorination of **1** with catalyst **P3**. Reactions were run in benzene in the presence of 62 mM pyridine.

**Table I.** Relative Rates of Dehydrofluorination of 1 by EGDMA/MMA Templated Polymers

| polymer[a] | template acid | equivalents[b] | $k_{Pn}/k_{P1}$[c] |
|---|---|---|---|
| **P1** | $CH_3CO_2H$ | 1 | (1.0) |
| **P2** |  | 1 | 1.0 |
| **P3** |  **2** | 0.5 | 3.5 |
| **P4** |  | 0.5 | 1.0 |
| **P5** |  | 0.33 | 2.5 |

[a] Polymers are prepared from a standard polymerization solution of EGDMA (80 mol %), MMA (17 mol %), and **3** (3 mol %) in DMF (50% by volume). Polymerization is initiated by AIBN (1 mol %). [b] Ratio of moles of template acid to moles of *N*-(2-aminoethyl)methacrylamide (**3**) in the polymerization solution. [c] $k_{P1} = 0.011$ h$^{-1}$ at 25 °C.

prepared employing mono-, di-, and tricarboxylic acid templates. Polymers were prepared from a standard polymerization solution containing 3 mol % of *N*-(2-aminoethyl)methacrylamide (**3**). The stoichiometry of the added template acid was controlled to maintain a 1:1 ratio of amine to carboxylic acid groups in the polymerization mixture. All polymers therefore contained the same total equivalents of amine per gram of polymer. Table I shows the catalytic performance of the resulting polymers.

Reactions were run in benzene under conditions of excess substrate to allow turnover (ratio of polymer-bound amines to **1** was 1:15). Under these conditions, pyridine was needed to scavenge the hydrofluoric acid produced during the reaction (pyridine does not affect the background reaction with **1**). Only templates possessing the 1,3-dicarboxylic acid group showed a catalytic rate faster than the control polymer (**P1**). The *size* of the template acid had no effect on the polymer's catalytic activity (**P1** and **P2**). Of particular interest is the polymer **P4**, made with a template that misdirects the basic amino group away from the substrate's $\alpha$-proton. This template creates a catalyst that performs no better than the control. Moreover, the template of **P5**, which misdirects a smaller portion of the amino groups, creates a catalyst of intermediate performance. These results suggest not only that the amino groups of **P3** and **P5** cooperate in the dehydrohalogenation reaction but also that functionality at the catalytic site of templated polymers can be manipulated in a rational and predictable fashion.

Optimization of initiator/porogen levels improved the performance of **P3**. Figure 1 shows the pseudo-first-order plot of **P3** and **P1** using an excess of **1** in benzene (ratio of **1** to polymer-bound amine is 17:1). Also shown in Figure 1 is the homogeneous reaction of **1** in the presence of *N*-(2-aminoethyl)acetamide (**4**). Under the reaction conditions, $k_{P3}/k_{P1}$ is 7.5 ± 0.3. The catalyst **P3** shows a rate constant 12.8 times greater than that observed for the homogeneous elimination reaction of **1** in the presence of **4**. Polymer **P3** also shows turnover. Data collected in Figure 1 ranges over 7 turnovers for **P3**.

Polymer **P3** exhibits Michaelis–Menten kinetics in *benzene* solvent with a $K_m$ of 27 mM and a $k_{cat}$ of $1.1 \times 10^{-2}$ min$^{-1}$ (Figure 2). In comparison, an antibody designed to catalyze the dehydrofluorination of **1** in *water* shows a $K_m$ of 0.182 mM and a $k_{cat}$ of 0.193 min$^{-1}$.[15] We have also observed that diethyl benzylmalonate exhibits inhibition of **P3** but not of the control polymer (**P1**). The rate of dehydrofluorination by **P3** drops 16 ± 5% upon the addition of a 5-fold excess of diethyl benzylmalonate to **1**.[22]

In conclusion, we have demonstrated that templated polymers can be designed to function as catalysts. The approach permits the introduction and manipulation of *known* functional groups at the active site. Their compatibility with organic solvents and ability to withstand harsh reaction conditions are notable and complementary to designed protein catalysts.

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**Supplementary Material Available:** Tables of X-ray data for bis(ethylammonium) benzylmalonate and synthetic procedures (16 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(21) The $E^2$ elimination in *homogeneous* solution decreases dramatically as the solvent polarity decreases. (a) Ingold, C. K. *Structure and Mechanism in Organic Chemistry*, 2nd ed.; Cornell University Press: Ithica, NY, 1969; pp 457, 680.

(22) The inhibition experiment was run in benzene solvent at 33 mM substrate and 166 mM diethyl benzylmalonate. $K_{P3}$ drops from 0.025 h$^{-1}$ to 0.021 h$^{-1}$. The control polymer, **P1**, is not affected by the addition of comparable amounts of diethyl benzylmalonate.