Template Synthesis of Macromolecules. Synthesis and Chemistry of Functionalized Macroporous Polydivinylbenzene[1]

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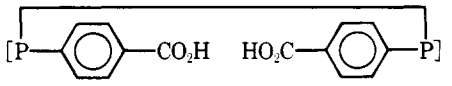
Abstract: The synthesis and characterization of several macroporous polydivinylbenzene copolymers are described. Copolymers of 1,6-hexylbis(*p*-vinylbenzoate) (**1**) and of [^{14}C=O]-1,6-hexylbis(*p*-vinylbenzoate) with divinylbenzene are used to establish the template synthesis method as a means of introducing sites of multiple functionality, i.e., i, on a surface of highly



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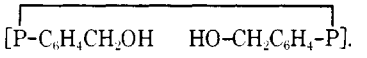

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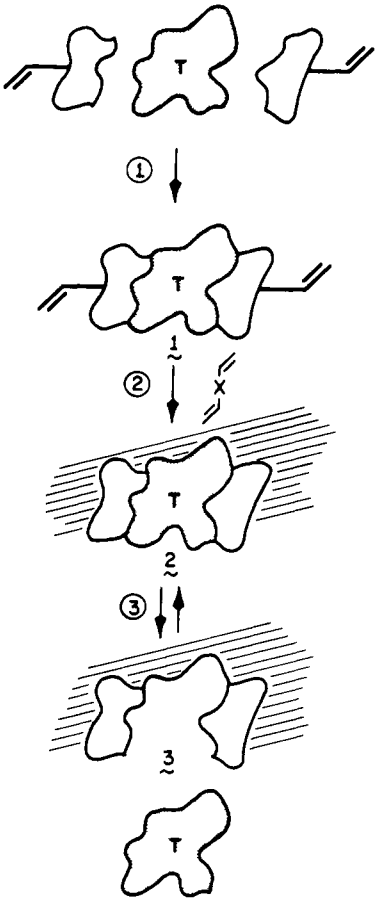
cross-linked polydivinylbenzene. Hydrolysis of a copolymer of bis(vinylbenzyl) *trans*-1,2-cyclobutanedicarboxylate (**2**) and divinylbenzene produces "doublets" of covalently bound benzyl alcohol groups, ii. Rebinding experiments with a difunctional reagent, fumaryl chloride, of similar geometry to the template molecule (*trans*-1,2-cyclobutanedicarboxylic acid) suggest that the benzyl alcohol functional groups retain some of the stereochemical information originally present in the cyclobutane diester.

Introduction

Because of the selectivity and efficiency of enzymes there has been considerable interest in the synthesis of organic substances that in some way simulate enzyme action. Enzyme activity is dependent, in part, upon a precise stereochemical relationship of catalytically active functional groups at the active site. One of the more challenging problems in the design of enzyme analogue systems is the selective introduction of organic functionality in a stereorational manner and maintenance of the stereochemical integrity of the functional groups over a period of time. There have been a number of ingenious approaches employed towards the solution of this problem.[2] Our work in this area was stimulated by the pioneering efforts of Wulff and co-workers who developed a general method for the controlled introduction of multiple organic functionality in organic polymers.[3,4] The technique, which we term the template synthesis method, is outlined in Scheme I. A template assembly (**1**) synthesized from two functionalized vinyl monomers that are joined together by a template molecule (T) (step 1) is copolymerized with a large excess of cross-linking reagent (step 2). Polymerization results in the formation of a three-dimensional polymeric matrix interspaced by an occasional template assembly (**2**). Hydrolysis removes the template molecule (step 3), which liberates the incipient functionality to produce regions of multiple functionality on the macromolecule (**3**). Provided that the hydrolysis (step 3) does not introduce gross structural deformations in the macromolecule, the hydrolyzed polymer can exhibit a "memory" for the original template molecule (T).

The present paper describes the synthesis of several copolymers prepared by the template synthesis method. The physical and chemical properties of these highly cross-linked macromolecules are discussed. In addition, we have established conditions necessary for hydrolysis of these macromolecules which produce "sites" of multiple functionality. These sites are subsequently utilized to rebind substrates that have a similar geometry to the original template molecule. In addition, these polymers are subjected to chemical transformations that probe the local environment of the functionality. Our studies suggest that functional groups introduced by the template synthesis method retain some of the stereochemical information originally present in the template assembly.

Scheme I



Results and Discussion

A. Polydivinylbenzene. Macromolecules prepared by the template synthesis method contain at least 55% cross-linking monomer. The physical properties of the polymer will be determined to a large degree by the choice of cross-linking reagent. The macromolecules described in this report are prepared from a technical grade of divinylbenzene (DVB). Our

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Table I. Surface Characteristics of Solvent-Modified Polydivinylbenzene

inert diluent	F_m[a]	av pore diameter, μ[b]	net pore volume, cm^3/g[b]	surface area, m^2/g[b,c]	mequiv double bonds/g	double bonds/cm^2
CH_3CN	0.49			250	1.35	3.25×10^{13}
CH_3CN	0.46	0.048	1.08	300	1.27	2.54×10^{13}
toluene	0.49	0.022	0.63	600		

[a] F_m = volume of monomer/volume of monomer + diluent. [b] Determined by mercury penetration porosimetry. [c] BET absorption analysis.

choice of this monomer was influenced by its availability and low cost as well as by the number of desirable properties it would impart to the polymer. DVB consists of a mixture of meta and para isomers of ethylvinyl- and divinylbenzene (45:55) together with a trace (<1%) of *m*- and *p*-diethylbenzene. Polydivinylbenzene, formed by free-radical-initiated (AIBN) polymerization of technical grade divinylbenzene, is a highly cross-linked three-dimensional network of styrene-like residues. It is a brittle, glassy, amorphous substance that is insoluble in all organic solvents and chemically inert to a number of reagents.[6,7] In addition, the polymer is hydrophobic; the introduction of polar organic functionality into this hydrophobic environment will permit a crude approximation of the environment of functionality at the active site of certain enzymes.[8]

When polymerization of divinylbenzene is carried out in the presence of "inert" diluents, such as acetonitrile or toluene, a milky white, macroporous polymer results. This material has a high surface area and large internal pore volume.[9] At the high levels of cross-linking used to prepare these polymers we anticipated that subsequent reactions would occur at or slightly beneath the surface of the polymer. The macroporous state is desirable since it permits access to a large number of functional groups.

Electron micrographs show the macroporous polymers to be agglomerates of randomly packed microspheres.[10,11] The voids between these microspheres comprise a network of channels similar to those found in bone char or alumina. In polymers that contain a high mole fraction of divinylbenzene, these voids are a permanent skeletal feature and do not collapse upon removal of solvent.[12]

The physical and chemical properties of several macroporous divinylbenzene polymers are given in Tables I and II. Contained are typical values of pore volumes and surface areas for polymers used in our studies.

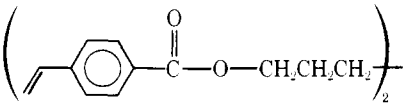
We have found that dry, macroporous polydivinylbenzene rapidly takes up a variety of organic liquids in the pores (Table II). It should be noted that the polymer exhibits little discrimination toward solvents of widely different polarity; the volume regain of toluene and methanol is virtually the same.[13,14]

An understanding of the chemical composition of the "surface" of polydivinylbenzene is extremely important for our studies, but one that is fraught with experimental difficulties. In addition to functionality that is intentionally introduced by the template synthesis method, the surface also contains a large number of unsaturated groups as a result of only partially polymerized divinylbenzene monomers and polymer chain ends. We have quantified the number of double bonds that are accessible to chemical reagents using procedures that were developed for end-group analysis of polystyrene;[15,16] these results are included in Table I. The number of double bonds is quite large, i.e., 1.0–1.3 mequiv of double bonds/g of polymer. When this number is divided by the surface area, we arrive at the concentration or density of double bonds per gram of polymer; these values are also included in Table I. This concentration should be compared with the surface density of a monolayer film of straight-chain carboxylic acid (5×10^{14} molecules/cm^2).[17] The design of chemical transformations on the polymer surface must recognize the highly unsaturated nature of the surface and its potential susceptibility to oxidation and attack by electrophilic reagents.

Polydivinylbenzene suffers from several deficiencies as a matrix for these studies. It is structurally and chemically heterogeneous. This can give rise to gradations in chemical reactivity over regions of the polymer. Furthermore, as a result of this inhomogeneity, the distribution of functionality at the polymer-solvent interface is poorly defined. These disadvantages remain at present a complicating factor.

A final comment is in order regarding our choice of polymerization conditions. The most common procedure for polymerizing water-insoluble monomers involves suspension or emulsion techniques.[18] Both employ surfactants or emulsifying agents that partition the monomer in the suspending medium, usually water. The resulting polymer particles contain surface active ingredients at the surface. Since we anticipated that the chemistry of these macroporous polymers would be limited at or very close to the surface, these contaminants, even in small amounts, could have an important effect on the subsequent chemistry. It was our decision, therefore, to eliminate this potential complication by employing bulk polymerization techniques.

B. Functionalization of Polydivinylbenzene. Conventional methods of functionalizing macromolecules[19] cannot reliably establish proximate relationships between functional groups. The technique that we employ for the controlled introduction of multiple organic functionality, the template synthesis method, has been outlined in a preceding section. At this time we report the synthesis and chemistry of two functionalized polymers prepared by the template synthesis method, a copolymer of divinylbenzene and 1,6-hexylbis(*p*-vinylbenzoate) (**1**), and a copolymer of divinylbenzene and bis(*p,m*-vinylbenzyl) *trans*-cyclobutane-1,2-dicarboxylate (**2**). The co-



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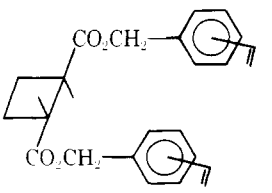

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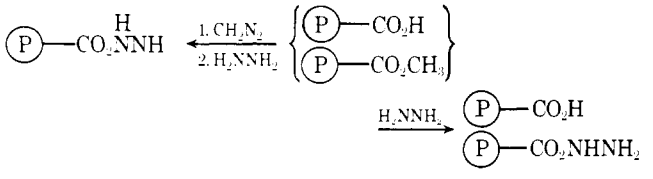
polymers are prepared with a low mole fraction of template monomer to divinylbenzene, typically 1–5 mol %. We reasoned that, at these low levels, the template assembly would not make a significant contribution to the gross structural rigidity of the polymeric solid; thus, hydrolysis of the template should not seriously disrupt the three-dimensional lattice. A second reason for the low level of loading stems from our desire to minimize the possibility of site–site interactions and focus on intrasite phenomena. These advantages, however, are won at the ex-

pense of the analytical problems that are encountered as a result of the low absolute number of functional groups.

Copolymer of Divinylbenzene and 1,6-Hexylbis(*p*-vinylbenzoate) (1). Bulk copolymerization of divinylbenzene and template assembly **1** (2.0 mol %) in the presence of toluene as inert diluent (F_m = 0.49) results in formation of a three-dimensional polymeric matrix interspaced with diesters of 1,6-hexanediol. The solid mass is crushed and sized (50–250 μ) and then washed thoroughly (CH_3OH) by continuous extraction to remove unreacted monomer. The infrared spectrum of this polymer (KBr) shows the ester carbonyl absorption ($\tilde{\mu}_{C=O}$ 1722 cm^{-1}) superimposed over polydivinylbenzene. A variety of hydrolysis conditions were examined to split out 1,6-hexanediol; the optimum condition for this polymer consists of hot aqueous methanolic HCl (1:1). After 8 h ~24% of the theoretical amount of 1,6-hexanediol was recovered; prolonged exposure to the reaction conditions did not appreciably increase this yield.[20] Assuming a uniform distribution of functionality on the surface, the hydrolyzed polymer contains 34.5 μmol of sites/g of polymer; dividing this number by the surface area yields the site density, 3.46×10^{12} sites/cm^2, which converts into an average of ≈3000 $Å^2$/site.

The fractional recovery of template molecules (24%) even after prolonged hydrolysis establishes that a significant number of template assemblies occupy regions that are inaccessible to the reagents used. These template assemblies may be buried in the interior of the highly cross-linked nucleus of polydivinylbenzene and be physically inaccessible to chemical reagents. Alternatively, low hydrolysis yields may result from a kinetic barrier to hydrolysis (or transesterification) because of the hydrophobic environment of the ester group. Regardless of the reason(s) for the low hydrolysis yield, the behavior of polydivinylbenzene is quite different from conventional gel-type styrene-divinylbenzene copolymers, which, at least in their swollen state, undergo reaction throughout the polymer network.[21]

Although we cannot be certain of the exact composition of the functional groups remaining on the polymer after hydrolysis, both chemical and spectroscopic evidence suggests that it consists of a mixture of carboxylic acid and methyl ester groups. The carboxylic acid groups cannot be titrated by conventional methods (KOH-EtOH) nor do they appear to be reactive with hydrazine. Hydrazine does, however, react with the methyl ester groups since we observe a decrease (20%) in the IR intensity of the carbonyl band of hydrolyzed polymer after treatment with H_2NNH_2. Treatment of hydrolyzed polymer with diazomethane followed by a hydrazine treatment results in a 30% decrease in intensity of the carbonyl band. When unhydrolyzed polymer is treated with hydrazine, the decrease in carbonyl intensity is also 30%. The hydrolysis yield calculated from the IR data (30%) is quite similar to the yield obtained by direct measurement of 1,6-hexanediol (24%).



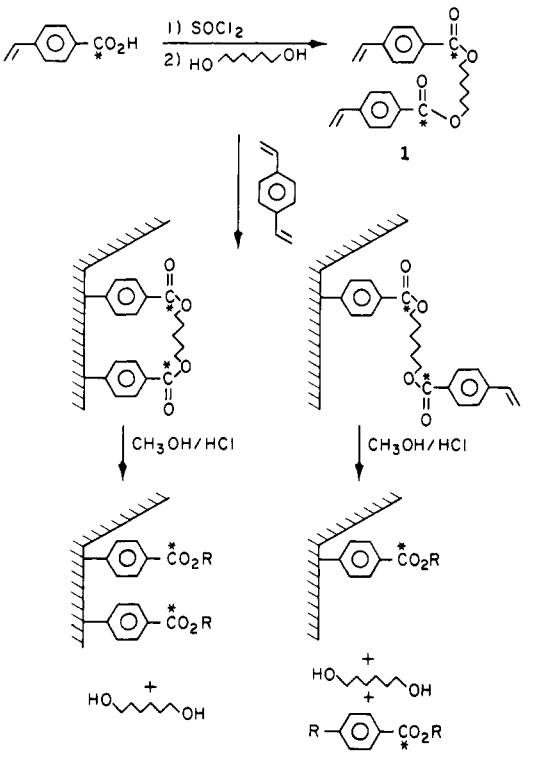
The manner in which the template assembly is incorporated into the macromolecule is extremely important. To ensure that the sites possess multiple functionality, a majority of the templates must be covalently bound to the macromolecule with both vinyl groups. We therefore undertook a study of the way in which the template assembly is bound to the macromolecule. We visualized three distinct situations that could result from copolymerization of a template assembly with divinylbenzene. The first is one where there is no covalent attachment of the template assembly to the macromolecule. A situation such as this could arise if the relative reactivities of the different monomers varied considerably. Since all monomers used in our study are styrene derivatives, the range of reactivity ratios is narrow (r_1:r_2 = 1 ± 0.3),[22] a situation that should result in a more or less random distribution of monomer units in the macromolecule.[23] The remaining possibilities involve incorporation of the template by either one or both of the vinyl groups into the bulk polymer; we will make reference to this as either one-point or two-point attachment.

Table II. Solvent Regain Experiments with Macroporous Polydivinylbenzene[a]

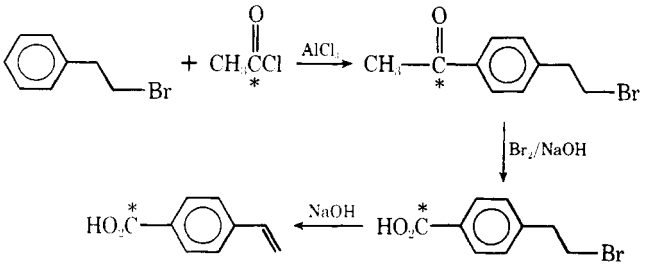
solvent	soaking time	solvent regain, mL/g of polymer[b]
toluene	5 days	1.23
methanol	10 min	1.23
	10 days	1.17

[a] Macroporous polydivinylbenzene was prepared with toluene as dilutent, F_m = 0.49. [b] Average value after centrifugation; see Experimental Section.

Scheme II



A distinction between all three types of binding can be made by the ^{14}C radiochemical labeling experiment illustrated in Scheme II. The ^{14}C-labeled diester (*) was prepared as outlined below; copolymerization with divinylbenzene was conducted in the usual manner. After the polymer was ground, continuous extraction (CH_3OH) liberates all material that is not covalently bound to the polymer. We found that <0.1% of the total radioactivity was recovered at this stage. If all of the template assemblies are incorporated by two-point attachment, hydrolysis of the polymer should not liberate any of the radioactivity. In practice, hydrolysis (HCl-CH_3OH) liberated 24% of the theoretical amount of 1,6-hexanediol with concomitant loss of only 0.3% of the total ^{14}C radiolabel. After correcting for the fractional recovery of 1,6-hexanediol and taking account of the statistical distribution of radiolabel, we can conclude the following: (1) an insignificant fraction of the template assemblies were not covalently bound to the polymer; (2) 3% of the template assemblies was covalently bound by



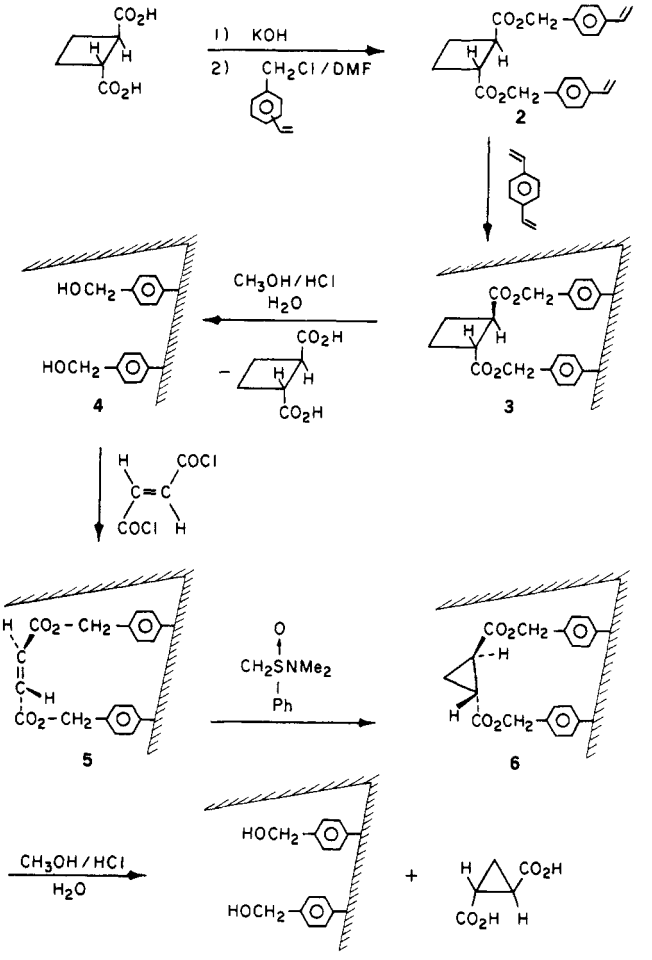
one-point attachment; (3) the vast majority (97%) of the templates are attached at both sites. We can conclude from these results that hydrolysis of polymers prepared by the template synthesis method produces sites of multiple functionality. The stereochemical relationship between the functional groups must, at least initially, be very similar to that which was present in the covalently bound precursor (diester). Tests which probe the maintenance of this stereochemical integrity after hydrolysis are the subject of the remainder of this study.

Copolymer of Divinylbenzene and Bis(*p,m*-vinylbenzyl) *trans*-Cyclobutane-1,2-dicarboxylate (2). To obtain additional information regarding the proximity of functional groups introduced by the template synthesis method *after* hydrolysis and to probe the local environment of this functionality, the sequence of experiments outlined in Scheme III was undertaken. It was our intention to introduce two benzyl alcohol groups at a "site" and to use these groups to covalently rebind a difunctional reagent to the polymer. Subsequent chemical transformations on the covalently bound substrate molecule would provide us with an opportunity to probe the local environment of the site.

Copolymerization of divinylbenzene with template **2** (3.8 mol %) using acetonitrile as cosolvent (F_m = 0.49) yields a macroporous polymer containing cyclobutanedicarboxylic acid diester groups (**3**). The infrared spectrum exhibits the expected ester carbonyl ($\tilde{\nu}_{C=O}$ 1736 cm^{-1}). Hydrolysis (refluxing 1:1 methanol–HCl, N_2, 8 h) liberates 30% of the total number of template assemblies. This produces 80 μmol of sites/g of polymer. The surface "concentration" of sites (1.9×10^{13} sites/cm^2 or 525 $Å^2$/site) for this polymer is somewhat higher than in the previous case. The sites produced upon hydrolysis presumably contain two polymer-bound benzyl alcohol groups. The presence of these functional groups is verified by treatment of **4** with trifluoroacetic anhydride; the resulting polymer exhibits a new IR absorption at 1788 cm^{-1} (trifluoromethylacetate group); control reactions with unhydrolyzed polymer did not produce this new absorption. The hydrolyzed polymer (**4**) contains "doublets" of benzyl alcohol groups scattered on the surface. Any three-dimensional relationship between these functional groups can be thought of as stereochemical information that has been imprinted on the polymer. This information originates from the initial stereochemical relationship present in the ester template assembly (**2**). We would like to determine how long, if at all, this information can be stored on the polymer and whether the information can be retrieved at a later time.

Reference to the temporal nature of the polymer surface is necessary since amorphous polymer structures, even in highly cross-linked polymers such as polydivinylbenzene, must be viewed in dynamic rather than in purely static terms. Even under ordinary conditions, the pendant polymer chains are in motion undergoing various changes in conformation and interchain organization.[24] The polymer surface structure is in a state of dynamic equilibrium with the extent of rotational and translational molecular motions being determined by pendant polymer chain length and the solvating medium in which the polymer is placed. If these factors were to dominate, prospects for information storage and retrieval would be dim. To assess

Scheme III



this possibility, we have examined the reaction of hydrolyzed polymer with difunctional reagents of similar geometry to the original template molecule, a situation that can lead to two point rebinding. Treatment of **4** with fumaryl chloride results in covalent attachment of the fumarate group to the polymer. The rebinding occurs by formation of new ester linkages between the polymer and the fumarate group. Ester rebinding is monitored by examining the change in intensity in the carbonyl region of the polymer before and after exposure to fumaryl chloride. The individual carbonyl absorptions of polymer-bound fumaric and cyclobutanedicarboxylic acid esters are not resolved; nevertheless, upon treatment of **4** with fumaryl chloride the expected increase in carbonyl intensity is observed. That fumaric acid is *covalently bound* to the polymer is established by the finding that the acid can only be liberated by a second hydrolysis (CH_3OH–HCl); the quantity of fumaric acid recovered indicates that 80% of the available sites in **4** have covalently bound the new template molecule. The uptake of fumaryl chloride is approximately equal to the theoretical mumber of *difunctional* sites and suggests that, at least in a significant number of cases, rebinding can occur in a manner similar to that which was found in the original polymer (two site). The observation that two-site rebinding dominates implies the benzyl alcohol groups, on the average, retain their stereochemical relationship. Additional confirmation of two-point rebinding comes from preliminary results with monofunctional reagents. When hydrolyzed polymer **4** containing 0.080 mmol/g of difunctional sites (benzyl alcohol groups) was treated with a monofunctional reagent, acetyl chloride, the rebinding yield amounts to 0.145 mmol/g or 91% of the total number of available alcohol groups.[25]

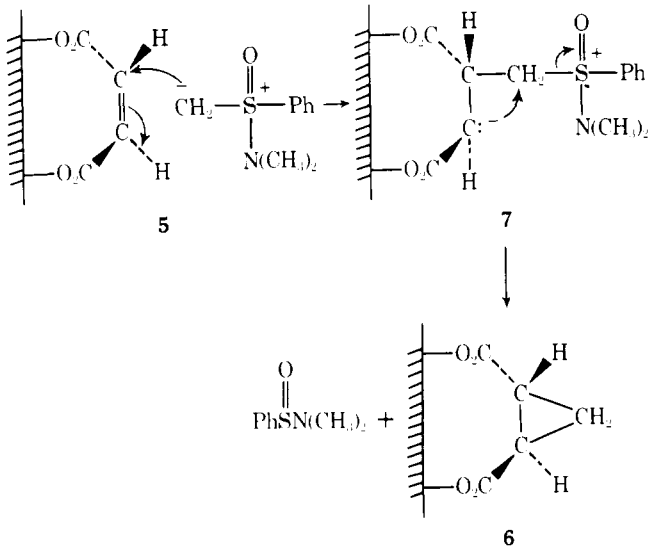
The region in which the hydrolysis and rebinding occur is

rather poorly defined. The area is at the interface between solvent phase and the highly cross-linked nucleus of the solid polydivinylbenzene. Located in this region are pendant polymer and vinyl groups, template assemblies, rebinding sites, and more lightly cross-linked segments of the polymer.[26] If the hydrolyzed polymer is to exhibit a "memory" for the template molecule (T), the template assembly must imprint stereochemical information at the polymerization stage. The sequence of experiments outlined above establishes the ability of the hydrolyzed macromolecule to rebind molecules that are similar to the original template.

Further chemical studies on the rebound fumarate group substantiate that a "memory" of the original template remains. The sequence of the experiments, outlined in Scheme III, involves at the penultimate step a methylene transfer to a prochiral alkene, fumaric acid, covalently bound to the macromolecule. When racemic template **2** is used for the polymer synthesis, racemic cyclopropanedicarboxylic acid would be the product from the methylenation step; however, when a chiral template is used for the polymer synthesis, the "memory" can take the form of local asymmetry in the region of the functional groups; this asymmetry may induce formation of a chiral product in the methylenation step. The polymer-bound fumaric ester (**5**) reacted with methylene-transfer reagents to form 1,2-cyclopropanedicarboxylic acid ester (**6**). This transformation was successfully executed using dimethylaminophenyloxosulfonium methylide as the nucleophilic methylene transfer reagent. Synthetic cyclopropanedicarboxylic acid is liberated by hydrolysis in 34% overall yield based upon available sites of the hydrolyzed polymer.

The preceding sequence was repeated using (−)-*trans*-1,2-cyclobutanedicarboxylic acid $[\alpha]^{25}_{D}$ −158.7° (CH_3OH)) as the template. After hydrolysis, rebinding of fumaryl chloride, cyclopropanation, and hydrolysis, *trans*-1,2-cyclopropanedicarboxylic acid was recovered as the dimethyl ester by preparative VPC. The diester exhibited a specific rotation $[\alpha]^{21}_{D}$ 0.1° which corresponds to a 0.05% enantiomeric purity (see Experimental Section).

The slight enantiomeric excess arises in the methylene-transfer step and must result from asymmetry in the vicinity of the reaction zone. The magnitude of the enantiomeric purity



is not surprising in view of the severity of the conditions required for hydrolysis of the template; prolonged hydrolysis no doubt results in some modification of the polymer surface and possible loss of asymmetry. In addition, the fumarate group is bound to the macromolecule by only two covalent linkages. The third point of reference must result from some unspecified interaction of the prochiral polymer-bound reaction complex **7** and its immediate surroundings.

The asymmetry in the reaction product arises from a very slight preference for attack of the methylene transfer reagent toward one face of the fumarate group. This slight preference can arise for a variety of reasons. Polymerization or copolymerization involving a chiral monomer can produce an asymmetric environment in the immediate vicinity of the chiral monomer. This asymmetric environment may result from a specific arrangement of neighboring pendant polymer chains, in which case asymmetry would, in time, dissipate as a result of the dynamic nature of the polymer surface. Asymmetry of this type would be sensitive to factors such as hydrolysis conditions, reaction solvents, and polymer lifetime.

A second possibility results in formation of a more permanent chirality in the vicinity of the template assembly. Chain transfer to divinylbenzene molecules generates a new chiral center. When the chain-transfer step takes place in the vicinity of a chiral template molecule, the rate of formation of the *R* and *S* configurations will differ. This can result in permanent local concentrations of asymmetric centers in the vicinity of the template molecule. The asymmetry that results from the preceding circumstances will be less sensitive to hydrolysis conditions providing the chiral center remains in proximity to the site of chemical reactivity.

The third possibility recognizes the fact that hydrolysis does not free all the chiral template molecules; indeed ~70% of the original chiral template molecules remain embedded in the polydivinylbenzene. The slight enantiomeric excess observed in the methylene-transfer step can be a result of the juxtaposition of an unhydrolzyed template assembly and rebound fumarate group.

It has recently been found that copolymerization of styrene with a chiral monomer produces asymmetry on the polystyrene backbone.[27] This important observation suggests that asymmetric induction during polymerization can, at least in part, be responsible for the origin of the optical activity in the cyclopropanation steps. Further studies on the storage and retrieval of stereochemical information on highly cross-linked macroporous polymers will be the subject of future reports.

Experimental Section

General. Infrared spectra were recorded on a Perkin-Elmer 283 spectrophotometer. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on either a Varian A56/60D, EM-360, or Bruker WH 90D spectrometer.

Gas chromatographic analyses were carried out on either a Hewlett-Packard 5710A or a Varian Aerograph Model 920 instrument. Peak area integrations were performed by electronic integration. The analysis of divinylbenzene mixtures was performed on a 6 ft × 1/4 in. glass 4.6% Bentone 34 + 3% silicone DC 550 on 60–80 mesh Gas-Chrom R (AW-DMCS) column at 105 °C.

Optical rotations were measured on a Perkin-Elmer 141 polarimeter, Zeiss polarimeter No. 53194, or Rudolph Instruments MP 7A41 photoelectric polarimeter.

^{14}C counting experiments were carried out using a Beckman LS 8000 scintillation counter. Labeled compounds were checked for purity by comparison with authentic samples of nonlabeled compounds. The ^{14}C-labeled acetyl chloride used as starting material was obtained from ICN.

Mercury intrusion porosimetry and BET surface area analysis was performed by Micromeritics Instrument Corp., Norcross, Ga. Elemental analyses were performed by Galbraith Laboratories.

Divinylbenzene was obtained commercially (Matheson Coleman and Bell) and was purified prior to polymerization by washing with aqueous NaOH (3×), water (2×) and sodium chloride followed by distillation under reduced pressure. The composition of this monomer after purification was determined by VPC: *m*-diethylbenzene (0.4%), *p*-diethylbenzene (0.2%), *m*-ethylvinylbenzene (28.9%), *p*-ethylvinylbenzene (12.6%), *m*-divinylbenzene (41.6%), and *p*-divinylbenzene (15.9%).

1,6-Hexanediol-*p*-vinylbenzoic Acid Diester (1).[28] To a solution of *p*-vinylbenzoyl chloride (5.0 g, 0.03 mol) in dry ether (100 ml) with triethylamine (6 mL) was added 1,6-hexanediol (1.77 g, 0.015 mol)

in dry ether (100 mL). After the mixture was stirred at room temperature overnight, the amine salt was filtered off and the resulting solution was washed (NH_4Cl, NaCl) and dried (Na_2SO_4). Removal of solvent under reduced pressure left a viscous liquid that solidified in the freezer. The solid was triturated with a small amount of pentane and then filtered to give 4.0 g (70%) of crude diester. Recrystallization (twice) from petroleum ether (30–60 °C) gave pure material: mp 73–75.5 °C; IR (KBr) $\tilde{\nu}_{max}$ 3062, 3040, 1710, 1610, 945, 849, 780, 710 cm^{-1}; NMR ($CDCl_3$) δ 8.05 (d, J = 8 Hz, 4 H), 7.5 (d, J = 8 Hz, 4 H), 6.86 (dd, J_{AX} = 16, J_{BX} = 10 Hz, 2 H), 6.0–5.15 (m, 4 H), 4.3 (t, J = 7 Hz, 4 H), 2.0–1.2 (m, 8 H). Anal. ($C_{24}H_{26}O_4$) C, H.

Bis(vinylbenzyl) *trans*-1,2-Cyclobutanedicarboxylate (2). *trans*-1,2-Cyclobutanedicarboxylic acid (7.9 g, 0.055 mol) dissolved in 100 mL of H_2O was treated with potassium hydroxide (85%, 7.26 g, 0.11 mol) and titrated with a potassium hydroxide solution (10%) to the phenolphthalein end point. Vacuum drying gave the dipotassium salt which was transferred to a N_2-flushed three-neck flask fitted with a condenser, mechanical stirrer, and addition funnel. Acetonitrile (100 mL) and 18-crown-6 (1.44 g, 0.005 mol) were added and the stirred suspension was treated with vinylbenzyl chloride (47 g, 0.3 mol; mixture of meta and para isomers, Dow Chemical). The mixture was heated (20 h, 55 °C), cooled, and filtered, and then stripped of solvent on a rotary evaporator.

Excess vinylbenzyl chloride was separated from the product by column chromatography on silica gel (4.5:1 petroleum ether–diethyl ether) to give 16.2 g (0.043 mol) of bis(vinylbenzyl) *trans*-1,2-cyclobutanedicarboxylate: 79% yield; NMR ($CDCl_3$) δ 7.33 (m, 4 H), 6.72 (q, $J_{AX} \simeq 17$, J_{AB} = 1.5 Hz), 5.11 (s, 2 H), 3.50 (m, 1 H), 2.17 (m, 2 H); IR (neat) ν_{max} 3085, 3050, 3000, 2980, 2950, 2880, 1738, 1725, 1240, 1160, 1095, 1050, 1014, 990, 910, 827, 799, 710 cm^{-1}. Anal. ($C_{24}H_{24}O_4$) C, H.

The chiral template assembly was prepared similarly with (−)-*trans*-1,2-cyclobutanedicarboxylic acid, $[\alpha]^{26}_D$ −161.5° (*c* 8.58, MeOH).

Divinylbenzene–Bis(vinylbenzyl) *trans*-1,2-Cyclobutanedicarboxylate Copolymer. A solution of bis(vinylbenzyl) *trans*-1,2-cyclobutanedicarboxylate (**1**, 8.0 g, 0.021 mol), freshly distilled divinylbenzene (70.1 g, 0.53 mol), acetonitrile (66.2 g, 1.61 mol), and AIBN (0.50 g, 0.0030 mol) was divided into two portions and placed in two medium-walled glass tubes which had constricted necks for sealing. The tubes were degassed on a vacuum line through five consecutive freeze–thaw cycles. The tubes were sealed on the line, covered with wire gauze, and placed in an oil bath where they were incubated at 70–75 °C for 12 h and then at 115 °C for 20 h.

The tubes were cooled and broken open, and the white crumbly polymer was ground up with mortar and pestle. The polymer was sized by sieving. Fractions of 60–200 mesh (75–250 μ) and >200 mesh (<75 μ) were collected. These were washed in the Soxhlet extractor with methanol for 2 days. The polymer was then removed and dried under vacuum: IR (KBr) ν_{max} 3020, 2970, 2925, 1744, 1738, 1601, 1484, 1445, 1150, 900, 790, 704 cm^{-1}.

The copolymer of 1,6-hexanediol-*p*-vinylbenzene acid diester (**1**) and divinylbenzene was prepared in a similar manner: IR (KBr) $\tilde{\nu}_{max}$ 1732 cm^{-1}.

Polymer Hydrolysis. A typical hydrolysis, using the copolymer of divinylbenzene and bis(vinylbenzyl) *trans*-1,2-cyclobutanedicarboxylate (**2**) as an example, is given below.

Approximately 1 g of dry polymer (60–200 mesh, 0.27 mmol of template/g of polymer) was weighed into a flask. A weighed amount (~20–30 mg) of succinic acid was added as a control to monitor nonspecific binding with the polymer. Methanol and concentrated HCl (1:1) were added and the solution was refluxed under nitrogen for 12 h. The polymer was collected by filtration while the solution was still hot. Hot methanol (100 mL) was used to wash the polymer. The combined filtrate was evaporated to dryness under vacuum. A weighted amount of dimethyl glutarate was added as an internal standard. An ethereal solution of diazomethane was added dropwise until a yellow color persisted. Gas chromatographic analysis was performed directly on this solution on a 2 m × $^1/_8$ in. column packed with 10% SE-30 on Chrom W-AW-DMCS (60–80 mesh). The yield of dimethyl *trans*-1,2-cyclobutanedicarboxylate was based upon the dimethyl glutarate standard. Insignificant losses were encountered owing to nonspecific binding using the above procedure. The average yield (six hydrolyses) of cyclobutanediester is 0.081 mequiv/g (30%).

Rebinding of an Acid to the Polymer via an Acid Chloride. Approximately 1 g of previously hydrolyzed polymer was dried under vacuum overnight and then weighed. This was placed in a flask with 100 mL of dry ether (distilled from sodium–benzophenone). A septum was fitted to the flask and 0.50 ml of the acid chloride was added via syringe. The flask was placed on a wrist action shaker overnight. The polymer was then collected under N_2 on a filter, washed with 100 mL of dry ether, and dried under vacuum. The rebinding yield was established by a hydrolysis procedure as described above. Control experiments using unfunctionalized macroporous polydivinylbenzene gave <1% of carboxylic acid upon hydrolysis.

Binding of Template Assemblies in Polydivinylbenzene ^{14}C-Labeling Experiments. [^{14}C=O]-*p*-Vinylbenzoyl chloride was prepared from phenethyl bromide and [^{14}C=O]acetyl chloride (ICN) according to literature procedures.[29] [^{14}C=O]-1,6-hexanediol bis(*p*-vinylbenzoate) (294 μCi/mol), prepared from [^{14}C=O]-*p*-vinylbenzoyl chloride and 1,6-hexanediol, was copolymerized with divinylbenzene with toluene as diluent as described previously. The resulting polymer activity, based upon weight of monomer and specific activity of the template assembly, is calculated to be 94.3 dpm/mg of polymer. The measured activity, obtained by gel suspension of finely powered polymer samples, resulted in an activity of 88.3 dpm/mg polymer, or 93.7% of the calculated activity. This smaller number is used in subsequent calculations for calculation of the percent loss of label.

Noncovalently Bound Template Assembly. The polymer was crushed and wet sieved (ethanol) and transferred to a Soxhlet thimble and extracted with CH_3OH for 24 h. The solvent was concentrated and the resulting solution passed through a millipore filter and then diluted with a toluene scintillation cocktail. The activity in the residue was 0.085 dpm/mg of polymer extracted which represents 0.09% nonincorporation of radiolabel. Loss of activity during hydrolysis was determined by hydrolyzing duplicate weighed samples of polymer in refluxing CH_3OH–HCl (24 h). Following filtration and concentration, the samples were analyzed by VPC for yield of 1,6-hexanediol (24%) and then diluted with cocktail. Each sample was counted in triplicate. The two samples yielded an activity of 258 and 283 dpm/g, respectively. The mean value of activity loss is 0.028% of the calculated polymer activity. Assuming monolabeled diester and recognizing that only 24% of the template assemblies hydrolyzed, the degree of one-point binding is calculated to be 2.8%.

Cyclopropanation of Polymer-Bound Fumarate Groups. A solution of (dimethylamino)methylphenyloxosulfonium tetrafluoroborate[30] (6.8 g, 0.025 mol) in dry Me_2SO was added to sodium hydride (1.05 g, 0.025 mol) under N_2 with efficient stirring. After gas evolution subsided, an additional 100 mL of dry Me_2SO was added. The stir bar was removed and a suspension of hydrolyzed polymer (20.8 g, 1.5 mmol of template) in dry Me_2SO (300 cm^3) was added. The flask was agitated with a wrist action shaker for 16 h. The polymer was filtered, washed with dry Me_2SO (100 mL) and methanol (2×), and then dried under vacuum. Hydrolysis and workup were carried out as described previously. The yield of cyclopropanedicarboxylic acid (65.8 mg, 195 mg theory) amounts to 34% yield based upon two-site rebinding of fumaric acid. When the polymer, obtained by hydrolysis of optically active cyclobutanedicarboxylic acid, was treated as above, dimethyl cyclopropanedicarboxylate was collected by preparative VPC. Its chemical purity was established by VPC; this sample had a specific rotation, $[\alpha]_D$ 0.98° (*c* 7.15, acetone), which corresponds to a 0.05% enantiomeric) excess, based upon a rotation of optically pure dimethyl ester of $[\alpha]^{25}_D$ 200° (acetone).[31]

Resolution of (±)-*trans*-1,2-Cyclobutanedicarboxylic Acid. A solution of (±)-*trans*-cyclobutanedicarboxylic acid (21.6 g, 0.15 mol) in 95% ethanol (100 mL) was heated to boiling and then slowly added to a hot solution of quinine (102.9 g, 0.30 mol) in 95% ethanol (250 mL). The combined solutions were boiled for an additional minute. The solution was allowed to cool slowly. After 4 days the crystals were collected. Three additional recrystallizations gave $[\alpha]^{21}_D$ −158.7° (CH_3OH), mp 111.5–113 °C (lit.[31] $[\alpha]^{25}_D$ −158°, mp 113–114 °C).

Solvent Regain Experiments. A weighed sample of polymer (75–250 μ), previously dried in a vacuum oven for 2 days, was placed in a flask with enough solvent to cover the polymer particles completely. After the specified soaking time had elapsed, the polymer was removed and placed in the top half of a centrifuge tube which had a glass frit of medium porosity dividing the top half from the bottom. A removable plug sealed with an O ring allowed easy removal of the solvent from the bottom of the tube following centrifuging. A small hole in the glass wall directly below the frit permitted air displacement as the solvent

flowed through the frit into the bottom half of the tube. Following centrifuging, the "dried" polymer was removed and weighed immediately and then dried to a constant weight in a vacuum oven and weighed again. The difference in weight between the polymer immediately after centrifuging and after drying to a constant weight represents the absorbed solvent and is reported in Table II as milliliters of solvent/gram of polymer. The polymer after centrifuging was almost free flowing; we did not therefore attempt to correct for interstitial solvent.

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