Synthesis and Chiral Recognition Ability of a Cross-Linked Polymer Gel Prepared by a Molecular Imprint Method Using Chiral Helical Polymers as Templates

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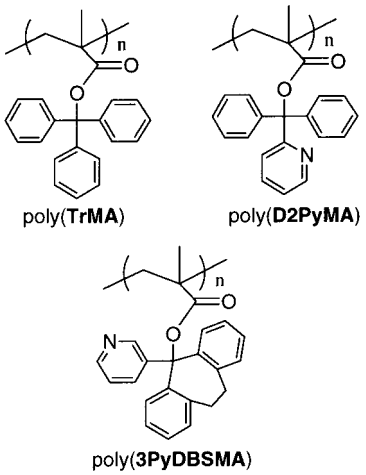
Received November 10, 2000
Revised Manuscript Received February 7, 2001

Introduction. Molecular imprinting, pioneered by Wulff,[1,2] is an effective method to prepare chiral, cross-linked polymer materials and has been extensively studied by several groups.[3−6] This method generally consists of the radical copolymerization of a monofunctional monomer with a bifunctional monomer (cross-linker) in the presence of a nonpolymerizable template and removal of the template by washing the gels.[5] An alternative method involves the cross-linking polymerization of a monomer with a detachable chiral moiety and removal of the chiral moiety by chemical reaction.[1,3] The obtained gels may have cavities whose shapes reflect the structure of the template molecule. The gels obtained by the template methods are known to show chiral recognition ability toward some racemates.

In the present study, we used three optically active, single-handed helical polymethacrylates having highly isotactic main-chain configuration,[7] namely, (+)-poly(triphenylmethyl methacrylate)[8] [poly(TrMA)], (+)-poly(diphenyl-2-pyridylmethyl methacrylate)[9] [poly(D2PyMA)], and (+)-poly(3-pyridyldibenzosuberyl methacrylate)[10] [poly(3PyDBSMA)], as template molecules. Single-handed helical polymethacrylates are known to exhibit chiral recognition ability toward a wide variety of racemates when used as a stationary phase for HPLC, and the recognition is considered to be governed by the chiral surface of the helical polymers.[11−14] If the helical chirality is imprinted into a polymer gel, the gel may resolve various racemates as efficiently as the helical polymethacrylates. Such a gel would be a more useful material than the template polymers themselves because of its chemical durability which some of the template helical polymers lack. The chiral recognition ability of the helical polymethacrylates has been reported to be gradually lost by solvolysis of the side-chain ester linkage by methanol, an effective solvent for chiral HPLC, leading to a loss of helical conformation.[11,13] To our knowledge, the molecular imprinting using a chiral polymer as a template has not yet been reported.

Experimental Section. Materials. The single-handed helical polymethacrylates were synthesized by anionic polymerization of the corresponding monomers using the complexes of *N,N′*-diphenylethylenediamine monolithium amide as initiators based on our previous study. (+)-Poly(TrMA)[8b] was obtained using (+)-2,3-dimethoxy-1,4-bis(dimethylamino)butane as the ligand and the benzene−hexane (1/1)-insoluble, oligomer-free part of the polymer ($[\alpha]_{365}$ +1403°, $[\alpha]_D$ +352°, DP = 47, M_w/M_n = 1.10) was used as template. (+)-Poly(D2PyMA)[9a] ($[\alpha]_{365}$ +1406°, DP = 30, M_w/M_n = 1.15) and (+)-poly(D3PyMA)[10] ($[\alpha]_{365}$ +1413°, DP = 26, M_w/M_n = 1.10) were synthesized using (+)-1-(2-pyrrolidinylmethyl)pyrrolidine as the ligand. The monomers and solvents for the gel synthesis were purified in the usual manner.



Gel Synthesis. The monomer, cross-linker, initiator, and template polymer were dissolved in solvent, and the solution was heated or irradiated using a high-pressure UV lamp. The obtained gel was dried under high vacuum at 60 °C and the unreacted monomer or cross-linker was removed. The yield of gel (radical polymerization) was determined by gravimetry.

Results and Discussion. The conditions and results of the gel syntheses are summarized in Table 1. In the gel synthesis using (+)-poly(D2PyMA) and (+)-poly(3PyDBSMA), methacrylic acid or acrylic acid was used as the monomer that would interact with the side chain pyridyl group through hydrogen bonding. In all the reactions, the product was obtained in high yield and the product was insoluble in the solvents, indicating the formation of a cross-linked gel. The template polymer was removed from the gel by refluxing the well-ground gel in a $CHCl_3$−methanol (1/1) mixture containing a small amount of aqueous HCl. Under this condition the template polymers are known to be completely solvolyzed into poly(methacrylic acid), which is soluble in methanol. The removal of the template was confirmed by IR spectroscopic analysis, which indicated complete disappearance of the adsorptions due to the ester groups and phenyl groups, and also by gravimetry.

To confirm the chiral induction during gelation by the effect of the template helical polymers, the optical activity of the template-free gels was measured. Because the gels were insoluble, the optical activity was measured in a transparent suspension[15] which was prepared by mixing the finely ground gel with a solvent having the same refractive index with that of the gel (see footnotes to Table 1 for the solvents). This method of optical activity measurement was tested by the following two experiments. First, a gel was synthesized using

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10.1021/ma001933i CCC: $20.00
Published on Web 03/10/2001

Table 1. Synthesis of Chiral Gel Using Helical Polymethacrylates as Template Molecules[a]

run	template (concn, M)	cross-linker (concn, M)	monomer (concn, M)	initiator (concn, M)	solvent	temp, °C	yield, %	$[\alpha]_\lambda^{25}$, deg
1	(+)-poly(TrMA) (0.16)	DVB[b] (2.0)	ethylstyrene[c] (1.6)	AIBN[d] (0.037)	THF	60	>99	+41[e] (λ = 589)
2	(+)-poly(TrMA) (0.55)	EDMA[f] (3.4)	MMA (1.8)	AIBN[d] (0.057)	THF	60	96	0[g] (λ = 589)
3	(+)-poly(D2PyMA) (0.032)	EDMA[f] (2.1)	methacrylic acid (0.44)	(*i*-PrOCOO)$_2$ (0.031)	$CHCl_3$	40	>99	+105[h] (λ = 365)
4	(+)-poly(D2PyMA) (0.11)	EDMA[f] (1.5)	methacrylic acid (0.12)	(*i*-PrOCOO)$_2$ (0.026)	$CHCl_3$	40	>99	+67[i] (λ = 365)
5	(+)-poly(D2PyMA) (0.15)	EDMA[f] (3.7)	methacrylic acid (0.15)	AIBN[d,j] (0.051)	$CHCl_3$	0	>99	n.d.[k] (λ = 365)
6	(+)-poly(3PyDBSMA) (0.13)	EDMA[f] (2.1)	methacrylic acid (0.44)	(*i*-PrOCOO)$_2$ (0.031)	$CHCl_3$	40	96	−250[l] (λ = 365)
7	(+)-poly(3PyDBSMA) (0.23)	EDMA[f] (3.9)	methacrylic acid (0.23)	(*i*-PrOCOO)$_2$ (0.053)	$CHCl_3$	40	94	−41[m] (λ = 365)
8	(+)-poly(3PyDBSMA) (0.13)	EDMA[f] (2.1)	methacrylic acid (0.44)	benzoyl peroxide[j] (0.031)	$CHCl_3$	0	92	−462[n] (λ = 365)
9	(+)-poly(3PyDBSMA) (0.13)	EDMA[f] (2.1)	acrylic acid (0.44)	(*i*-PrOCOO)$_2$ (0.031)	$CHCl_3$	40	89	−27[o] (λ = 365)
10	(+)-poly(3PyDBSMA) (0.27)	EDMA[f] (4.3)	acrylic acid (0.90)	(*i*-PrOCOO)$_2$ (0.064)	$CHCl_3$	40	90	−152[o] (λ = 365)
11	(+)-poly(3PyDBSMA) (0.13)	EDMA[f] (2.1)	acrylamide (0.44)	(*i*-PrOCOO)$_2$ (0.031)	$CHCl_3$	40	98	n.d.[k] (λ = 365)

[a] Cross-linker: 0.042 mol (run 1), 0.010 mol (run 2), 0.045 mol (run 3), 0.041 mol (run 4), 0.020 mol (run 5), 0.00186 mol (runs 6, 8-11), 0.00055 mol (run 7). Polymerization time = 48 h. [b] DVB = divinylbenzene (isomeric mixture). [c] Isomeric mixture. [d] AIBN = α,α′-azobisisobutyronitrile. [e] In a CH_2I_2−toluene (1.07/0.95, v/v) mixture. [f] EDMA = ethylene dimethacrylate. [g] In a CH_2I_2−toluene (0.48/1.54, v/v) mixture. [h] In a 1-bromonaphthalene−toluene (0.45/1.54, v/v) mixture. [i] In a 1-bromonaphthalene−toluene (0.53/1.47, v/v) mixture. [j] Under UV irradiation. [k] Not measured because transparent suspension was not obtained. [l] In a 1-bromonaphthalene−toluene (1.02/2.63, v/v) mixture. [m] In a 1-bromonaphthalene−toluene (0.95/2.50, v/v) mixture. [n] In a 1-bromonaphthalene−toluene (0.75/2.25, v/v) mixture. [o] In a 1-bromonaphthalene−toluene (0.75/2.50, v/v) mixture.

Table 2. Chiral Recognition by Chiral Gels Synthesized Using (+)-Poly(3PyDBSMA) as Template and by the Template Polymer[a]

run	racemate (analyte)	gel or template[b]	adsorbed analyte,[c] %	ee of free analyte in supernatant solution,[c] %	separation factor[d]
1	*trans*-stilbene oxide	gel of run 6 in Table 1	61	3.0 (−)	1.10
2	*trans*-stilbene oxide	gel of run 6 in Table 1e	62	0.6 (−)	∼1
3	*trans*-stilbene oxide	gel of run 6 in Table 1f	60	0.3 (−)	∼1
4	*trans*-stilbene oxide	gel of run 7 in Table 1	54	4.5 (−)	1.18
5	*trans*-stilbene oxide	(+)-poly(3PyDBSMA)	64	6.6 (+)	1.23
6	Tröger's base	gel of run 6 in Table 1	87	1.6 (−)	1.04
7	Tröger's base	gel of run 7 in Table 1	73	0.3 (−)	∼1
8	Tröger's base	(+)-poly(3PyDBSMA)	66	4.2 (+)	1.14
9	flavanone	gel of run 6 in Table 1	86	1.1 (−)	1.03
10	flavanone	gel of run 7 in Table 1	81	∼0	∼1
11	flavanone	(+)-poly(3PyDBSMA)	81	6.3 (+)	1.17
12	1-anthryl-2,2,2-trifluoroethanol	gel of run 6 in Table 1	92	1.7 (+)	1.04
13	1-anthryl-2,2,2-trifluoroethanol	gel of run 7 in Table 1	89	0.2 (+)	∼1
14	1-anthryl-2,2,2-trifluoroethanol	(+)-poly(3PyDBSMA)	94	3.1 (−)	1.07

[a] Experimetal conditions: gel or polymer 20 mg; racemic analyte 0.05 mg (100 μL portion from a 0.5 mg·mL^{-1} solution of **1** in hexane-2-propanol (95/5, v/v) (runs 1-8) or in hexane-2-propanol (9/1, v/v) (runs 9-14); temperature ca. 25 °C; time 3 h. [b] Finely ground with a mortar. [c] Determined by HPLC analysis of supernatant solution using a Chiralcel OD columun. Absorption yield was estimated by comparing the peak area of the sample in question with that of the stock solution of racemate. The error of ee estimated was less than 1% judging from the data for racemates. [d] Calculated accroding to $\alpha = (F_{major}(\%)/F_{minor}(\%))/(A_{minor}(\%)/A_{major}(\%))$, where F_{major} and F_{minor} are the percentages of major and minor isomers of free analyte in supernatant solution, respectively, and A_{major} and A_{minor} are those of major and minor isomers of adsorbed analyte, respectively.[8b] [e] The gel was methylated with CH_2N_2. [f] Template polymer was not removed from the gel.

racemic poly(TrMA) (DP = 45, M_w/M_n = 1.11)[16] under conditions the same as run 1 in Table 1 as a control experiment, and the optical activity of the gel after the removal of the template was measured in a suspension in a CH_2I_2−toluene (47.8/52.1, v/v)) mixture: the gel did not show significant optical activity. Second, optical activity of a commercial, achiral polystyrene-based gel, TSK G3000H (TOSOH), was measured in a suspension in a CH_2I_2−toluene (1.00/1.00, v/v) mixture to find no detectable rotation. Thus, the method of measurement employed in this work was shown to be reliable.

Most of the gels showed optical activity, indicating that the gels have a chiral structure. The magnitude and sign of the optical activity varied depending on the concentration of the monomers and the kind of monomers used for the gel synthesis for all the templates. However, no definite trend was observed in the data shown in Table 1 except that a lower polymerization temperature increased the optical activity of the gel as seen from runs 7 and 8.

The chiral recognition ability of the gels was evaluated by an enantiomer-selective adsorption experiment where a racemate and the gel are suspended in a hexane−2-propanol mixture (9/1 or 95/5) and the ee of the "free" analyte in the supernatant solution was determined by chiral HPLC. This experimental method has been reported in the literature.[10] As low-molecular-weight racemates, *trans*-stilbene oxide, Tröger's base, flavanone, and 1-anthryl-2,2,2-trifluoroethanol were employed. Among the gels obtained in this study, only those of runs 6 and 7 prepared from ethylene dimethacrylate and methacrylic acid in the presence of (+)-poly(3PyDBSMA) showed chiral recognition ability (Table 2). The reason for this is not immediately known, including why the gel of run 8 showing higher optical activity than that of run 6 prepared from the same monomer mixture using the same template did not resolve the racemates.

Though *trans*-stilbene oxide was resolved on both gels from run 6 and run 7 in Table 1, the other racemates were resolved only on the gel of run 6 in Table 1. The resolving power of the gels was lower than that of the template polymer itself. It is interesting that the gels and the template polymer ((+)-poly(3PyDBSMA)) predominantly absorbed opposite enantiomers. In addition, the gel of run 6 in Table 1 did not show any resolving

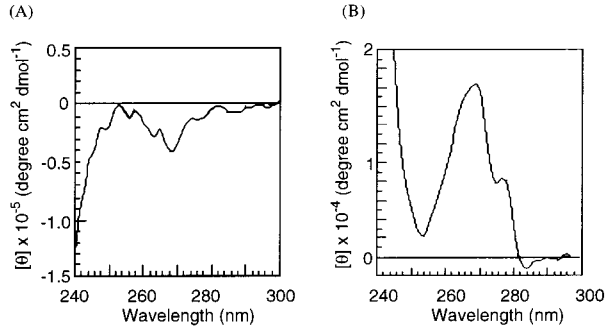

Figure 1. CD spectra of supernatant solution in the resolution of rac.-poly(3PyDBSMA) on the gel of run 6 in Table 1 (A) and that of (+)-poly(3PyDBSMA), the template polymer (B). The spectra were taken in $CHCl_3$ at ambient temperature.

power toward *trans*-stilbene oxide before the removal of the template (run 2 in Table 2). These findings indicate that the observed resolution is based on the chiral structure of the gel and not on the template polymer even if it might remain in a trace amount in the gel.

Another important observation was that the gel of run 6 in Table 1 lost its resolving power after it was treated with CH_2N_2 to methylate carboxylic groups originating from the methacrylic acid (run 3 in Table 2). The carboxylic groups seem to play a role in the resolution. In addition, when isooctane or hexane was used as the suspension solvent in place of the hexane−2-propanol mixture used in run 1 in Table 2, no resolution was achieved although a similar amount of analytes was absorbed onto the gel, indicating that 2-propanol may be involved in the resolution mechanism. Furthermore, the use of chloroform in place of hexane−2-propanol in run 4 resulted in no adsorption of analyte onto the gel.

The resolution of the racemic template polymer was also examined using the gel of run 6 in Table 1. As a racemic sample, an equimolar mixture of the right-handed helical and left-handed helical poly(3PyDBSMA) prepared by radical polymerization (DP = 38, M_w/M_n = 1.07, mm > 99%, $CHCl_3$-soluble part of the polymerization product using $(^i\text{PrOCOO})_2$ in toluene at 40 °C, run 4 in Table 2 in ref 8) was employed. When a solution of the racemic polymer (3.75 mg in 1.5 mL $CHCl_3$) was mixed with 120 mg of the gel for 5 min, 48% of the analyte polymer was adsorbed on the gel. The supernatant solution showed the opposite optical activity ($[\alpha]_{365}$ ca. −30°) to (+)-poly(3PyDBSMA) ($[\alpha]_{365}$ +1535° ($CHCl_3$)) and clear CD absorptions. The spectral pattern was very similar to that of the spectrum of the template (+)-poly(3PyDBSMA) and the sign of absorptions was opposite to that in the spectrum of the (+)-template (Figure 1). This indicates that the gel predominantly absorbed the (+)-isomer in the racemic polymer having the same helical sense as that of the template polymer. From the absorption yield and the CD intensity for the supernatant solution and for the (+)-polymer (supernatant solution: $[\theta]_{269}$ +410 deg·cm^2·dmol^{-1}; (+)-poly(3PyDBSMA): $[\theta]_{269}$ +18400 deg·cm^2·dmol^{-1}), the separation factor was calculated to be 1.09. These results suggests that the gel has chiral cavities which may have a shape similar to the template polymer in line with the concept of template polymerization.

Conclusions. Optically active cross-linked gels were synthesized by a template polymerization technique using the single-handed helical polymers as templates. The gel prepared using (+)-poly(3PyDBSMA) resolved low-molecular-weight racemates in addition to the racemic sample of the template polymer. Although the structure of the gel including the nature of the chirality and the mechanism of resolution are not yet clear, the results strongly suggest that the chiral structure of the helical template was "imprinted" into the gel. The template synthesis of a chiral gel using a synthetic chiral polymer is unprecedented.

Acknowledgment. This work was supported in part by NEDO under the Ministry of International Trade and Industry, Japan, through the grant for "Precision Catalytic Polymerization" in the Project "Technology for Novel High-Functional Material" (1996-2000), in part by Grant-in-Aid for Scientific Research (No.11750762) from the Ministry of Education, Science, Sports, and Culture, Japan, and in part by the Shorai Foundation, Japan. We thank Ms. Kiyoko Ueda (Nagoya University) for experimental assistance.

Supporting Information Available: Text giving experimental details for the synthesis in run 6 of Table 1 with figures showing the IR spectra of poly(3PyDBSMA), the gel containing the template, and the gel after removal of the template. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Poly(TrMA) was prepared by polymerization using *N,N′*-diphenylethylenediamine monolithium amide as initiator in THF at −78 °C at [TrMA]/[Li] = 20 for 24 h. Yield of MeOH-insoluble part was 80%, and the triad isotacticity was mm = 99%. The polymerization procedure reported in ref 8b was followed with modifications. [j] Under UV irradiation. [k] Not measured because transparent suspension was not obatined.

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