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Journal of Chromatography A, 906 (2001) 205–225

JOURNAL OF CHROMATOGRAPHY A

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Review

Optically active synthetic polymers as chiral stationary phases in HPLC

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Abstract

Synthetic, optically active polymers used as CSP are reviewed. The polymers are classified into three major categories, namely, addition polymers, condensation polymers, and cross-linked gels. The emphasis lies on polymethacrylates having helical conformation belonging to the first category. Helical polymethacrylates are synthesized using asymmetric anionic or radical polymerization techniques and show resolving ability towards a wide range of racemate.

Keywords: Reviews; Chiral stationary phases, LC; Polymers

Contents

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0021-9673/01/$ – see front matter
PII: S0021-9673(00)00944-4

1. Introduction

Synthesis of optically active polymers is an important field in macromolecular science as they find a wide variety of potential applications based on the chiral structure [1–8]. An important field of application is chiral recognition [9–20]. This ability of chiral polymers has been utilized in various forms of catalytic and separation chemistry. One of the most practical and widely accepted applications of chiral polymers is the use as chiral stationary phase (CSP) for high-performance liquid chromatography (HPLC) for the separation of racemic compounds (resolution). Various CSP's have been invented so far and some of them are commercialized and becoming indispensable material for separation in the fields of synthetic and medicinal chemistry. Although HPLC once used to be thought to be a method limited only to analytical scale, preparative scale resolution has also been made practical already.

There are three types of chiral polymers used as CSP: biopolymers [11–13,20], polymers prepared by modification of naturally occurring polymer backbones such as polysaccharides [11–18,20] and those having fully synthetic structure [9–13,19,20]. This article reviews the synthesis and performance as CSP of the latter type of polymers. The polymers are classified into three major categories by the type of polymerization, that is, (1) addition polymers including vinyl, aldehyde, isocyanide, and acetylene polymers, (2) condensation polymers including polyamides and polyurethanes, and (3) cross-linked gels. Emphasis will be given on the synthesis and application of helical polymethacrylates introduced and extensively studied by Okamoto's group [1–6,11–13,19,20]. The reviewed CSP's include not only those for HPLC but also the ones for chromatography in general.

2. Addition polymers

Several optically active linear polymers prepared by addition polymerization having chiral recognition ability are discussed in this section. Among them, single-handed helical polymethacrylates and poly(meth)acrylamides bearing chiral side groups are especially effective as CSP for HPLC and some of them are commercialized.

2.1. Helical polymethacrylates

2.1.1. Synthesis (Helix-sense-selective polymerization)

Helical polymethacrylates have significantly contributed to the area of polymer CSP and the synthetic aspects are still being actively studied which may lead to novel polymer CSP's in the future. The polymers reviewed here include also those whose chiral recognition ability has not yet been evaluated.

Triphenylmethyl methacrylate (**TrMA**) gives an almost completely isotactic polymerization by anionic polymerization either in a nonpolar solvent or in a polar solvent [21]. TrMA affords a highly isotactic polymer even through free-radical polymerization [22]. These are in contrast to the facts that the stereochemistry of anionic polymerization of conventional methacrylate monomers is generally strongly dependent on reaction solvent and vinyl polymerization by free-radical catalysis generally results in poor stereocontrol [23,24]. The isotactic specificity of **TrMA** polymerization is ascribed to helix formation of the main chain: the anionic or radical polymerization of **TrMA** gives an equimolar mixture of enantiomeric right- and left-handed helices. In 1979, Okamoto and coworkers reported that by anionic polymerization using a complex of *n*-BuLi with (−)-sparteine (Sp) at low temperature,

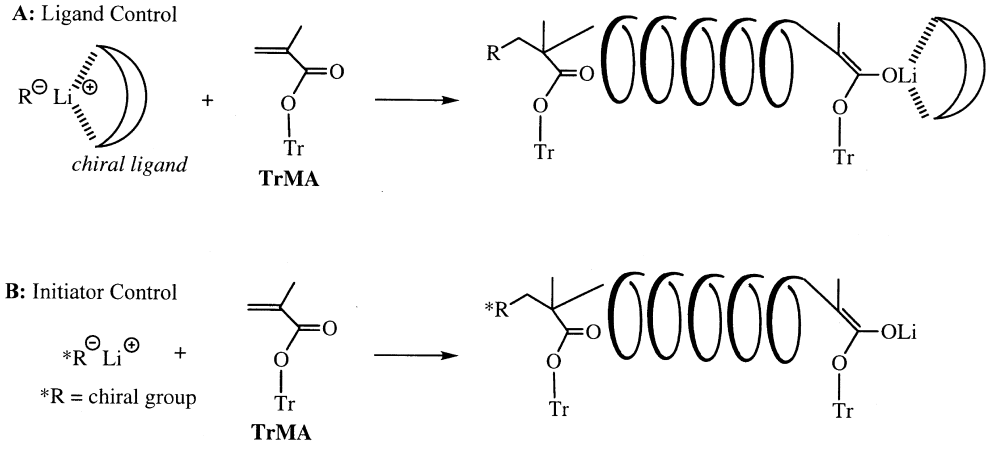


Fig. 1. Helix-sense-selective polymerization of **TrMA** using a complex of organolithium with chiral ligand (A) and using a chiral organolithium (B).

TrMA produces a highly isotactic polymer showing high optical activity and circular dichroism (CD) absorptions [25–31]. In this polymerization, one of the enantiomeric helices is selectively formed (helix-sense-selective polymerization) and the obtained polymer possesses a single-handed helical conformation of the main chain. The helical conformation is maintained by steric repulsion of the bulky side groups: hence, the conformation and chiroptical properties of poly(**TrMA**) is lost when the bulky trityl groups are removed from the main chain by hydrolysis of the ester linkage. Poly(**TrMA**) was the first vinyl polymer having such a conformation synthesized from an achiral (prochiral) monomer though poly(α-olefin)s with chiral pendent groups had been reported to take a helical structure with excess helicity [8].

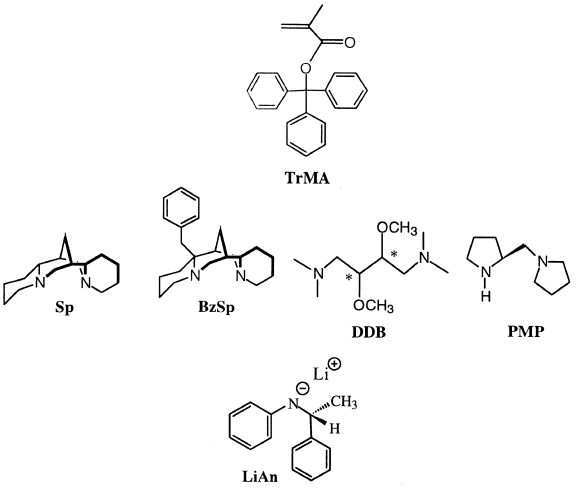
The asymmetric polymerization is carried out using a complex of an organolithium with a chiral ligand or using a chiral organolithium (Fig. 1)[9–11]. The helix-sense-selection is governed by the chirality of the ligand or the initiator (Fig. 1 A and B). Several chiral ligands including **Sp** [25,26,28,29], 6-benzylsparteine (**BzSp**) [32], 2,3-dimethoxy-1,4-bis(dimethylamino)butane (**DDB**) [27,28], and (+)-1-(2-pyrrolidinylmethy)pyrrolidine (**PMP**) [28] have been shown to control the stereochemistry of **TrMA** polymerization effectively. As a chiral organolithium, lithium (*R*)-*N*-(1-phenylethyl)anilide (**LiAn**) is known [25,26]. Ligand control affords a polymer with higher optical activity (helix-sense excess) than initiator control, and it is more effective in the polymerization in toluene than in THF (Table 1). The ligand is reasonably assumed to coordinate to

Table 1
Asymmetric polymerization of TrMA at −78°C[a]

Initiator	Solvent	Yield (%)	$[\alpha]_D$
Chiral organolithium			
LiAn	Toluene	73	−70°
LiAn	THF	93	−82°
Complex of organolithum with chiral ligand			
(−)-**Sp**-9-fluorenyllithium (FILi)	Toluene	99	+383°
(+)-**DDB**-9-fluorenyllithium (FILi)	Toluene	100	+344°
(+)-**PMP**-9-fluorenyllithium (FILi)	Toluene	100	+344°
(−)-**Sp**-*n*-BuLi	THF	100	+7°

[a] Data cited from Refs. [25] and [28].

the counter cation (Li^+) at the living growing end and makes a chiral reaction environment. In THF, the coordination of the ligand is inhibited by the coordination of the solvent, and therefore, the obtained polymer shows only small optical activity. Using enantiomers of commercially available **DDB**, polymers having opposite helicity can be produced [27].



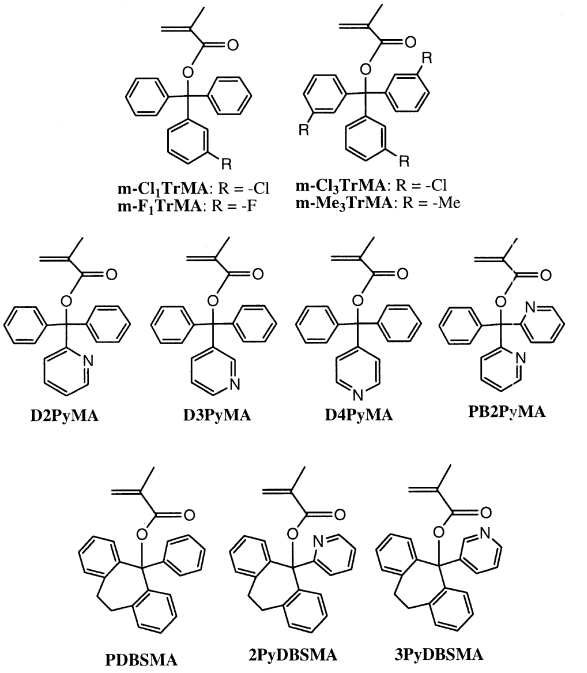


Fig. 2. Bulky methacrylates designed after **TrMA** in search of monomers with more stable ester linkage.

The stereochemical mechanism of the unique TrMA polymerization using the complexes of 9-fluorenyllithium (**FlLi**) with **Sp**, (+)-**DDB**, and (+)-1-(2-pyrrolidinylmethyl)pyrrolidine (**PMP**) has been investigated in detail by the analysis of the asymmetric oligomerization products [28–30]. The study revealed that the oligomeric propagating species having a degree of polymerization (DP) of five or larger are principally isotactic. Once the oligomeric species grows up to DP of ca. nine, a stable helix starts and monomer addition accelerates. Most of the oligomers of DP≥5 consist of purely one antipode of enantiomers: those obtained using **Sp-FlLi** have an ---*RRR*--- main-chain configuration while those prepared using (+)-**PMP-FlLi** and (+)-**DDB-FlLi** have an ---*SSS*--- configuration. On the basis of theses results, the three chiral ligands appear to regulate the main-chain absolute configuration as well as the screw sense of helix. However, the helix sense of the polymers obtained using the three ligands is considered to be the same because the signs of optical activity and circular dichroism absorption of the polymers coincide. This indicates that the prevailing helix sense is not governed by the main-chain configuration but mainly by the chirality of the ligands of initiator complexes in the process of polymerization.

Since the finding of the helix-sense-selective polymerization of **TrMA**, various **TrMA**-analogues have been synthesized with the interest in the influence of monomer structure on polymerization stereochemistry and on the chiral recognition ability of the resulting polymers. Regarding the performance as CSP, durability of the stationary phase is an important factor in addition to the resolving power. Although optically active poly(**TrMA**) can resolve various racemates, it has a weak point that the side-chain ester linkage is readily solvolized by methanol which is often a preferred eluent for HPLC [32,33]. In order to improve this point, several monomers were designed after **TrMA** (Fig. 2)

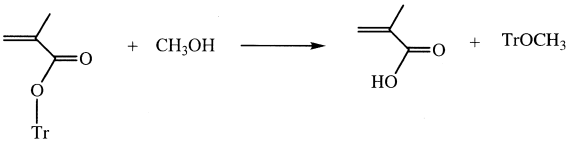


Fig. 3. Methanolysis of **TrMA**.

[22,35–46]. Since the solvolysis is considered to take place through a triarylmethyl cation (Fig. 3), it is important to design a triarylmethyl side group whose corresponding tertiary cation is less stable than trityl cation. This has been realized by (1) introducing electron withdrawing group(s) to phenyl group of trityl group, (2) replacing phenyl group(s) of trityl group with pyridyl group(s), or (3) tying two phenyl groups of trityl group with an ethylene group. The triarylmethyl cation is destabilized by electronic effects by methods (1) and (2) and a stable coplanar conformation of the two tied phenyl group in the cation becomes difficult by method (3). Durability of various monomers has been evaluated by monitoring the reaction shown in Fig. 3 directly by NMR spectroscopy. Pseudo first-order rate constant and half-life of each monomer are summarized in Table 2. The monomers designed to be durable showed higher resistance against methanolysis compared with TrMA: for example, tris(*m*-chlorophenyl)methyl methacrylate (**m-Cl_3TrMA**) [35], diphenyl-2-pyridyl methacrylate (**D2PyMA**) [39], and 1-phenyldibenzosuberyl methacrylate (**PDBSMA**) [45] corresponding the methods (1)–(3), respectively, were more slowly solvolized than **TrMA** under the same reaction conditions.

Introduction of a pyridyl group to the side chain of the monomer indeed improves the durability of monomer, but it created a new problem that the stereoregulation of polymerization is much more difficult when a monomer has a polar pyridyl group in the side chain [36]. This is because the interaction of the side-chain pyridyl group with the counter cation of the growing end competes with the effective coordination of chiral ligand. For example, diphenyl-2-pyridyl methacrylate (**D2PyMA**) gives a mixture of right- and left-handed helices by polymerization using **Sp** or **DDB** as a chiral ligand which affords completely single-handed helix in the polymerization of **TrMA**. After various chiral ligands were tested for the anionic polymerization of **D2PyMA** in search for a good condition for helix-sense selection, **PMP** was found to give a completely single-handed helical poly(**D2PyMA**) when used as a ligand [36,37]. In addition, polymerization using **PMP** led to polymers with narrow molecular mass distribution. **PMP** was also effective in controlling stereochemistry of polymerization of other pyridyl-group containing monomers (**D3PyMA** [40], **PB2PyMA** [41], **2PyDBSMA** [45], **3PyDBSMA** [46]). The successful stereoregulation by **PMP** has been ascribed to a tighter coordination of **PMP** than the other ligands to the growing enolate anion as shown in Fig. 4 [36].

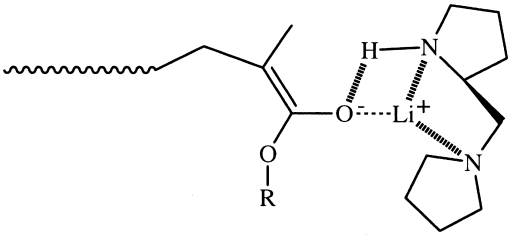
Also, the helical conformation optically active poly(**D2PyMA**) was less stable compared with that of poly(**TrMA**). The single-handed helix obtained by polymerization using **PMP** changed into a mixture of right- and left-handed helices through stereomutation (helix–helix transition) in solution [38].

PDBSMA is one of the monomers designed to be more durable than **TrMA** [22,42–45]. Similarly to **TrMA**, **PDBSMA** led to an optically active, single-handed helical polymer by asymmetric anionic polymerization using **Sp**, **DDB**, and **PMP** as chiral ligands [45]. It is interesting that the single-handed helical poly(**PDBSMA**) exhibits a ca. 20% larger

Table 2
Methanolysis of methacrylates[a]

Monomer	k[b]	Half-life period
	h^{-1}	min
TrMA	2.86	14.5
m-Me_3TrMA	13.0	3.2
m-F_1TrMA	0.21	198
m-CI_1TrMA	0.045	930
m-CI_3Rma	0.053	786
PDBSMA	0.466	89.0
D2PyMA	0.0256	1620
D3Yma	0.0291	1439
PB2PyMA	1.24×10^{-5}	335×10^{4}
2PyDBSMA	0.0165	2520
3PyDBSMA	0.0444	936

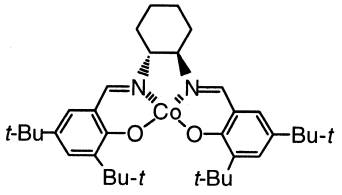
[a] Measured in $CDCI_3$-CD_3OD (1:1) mixture at 35°C. Data cited from Refs. [34], [39], [45] and [46].
[b] Pseudo first-order rate constant.



R = bulky triaryl methyl group

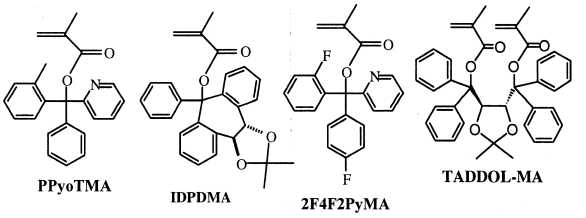
Fig. 4. A tight coordination of PMP to growing end of polymethacrylate anion.

specific rotation ($[\alpha]_{365}+1780°$) than poly(**TrMA**). **PDBSMA** gave an almost completely isotactic polymer even by conventional radical polymerization, meaning that the radical polymerization product is an equimolar mixture of right- and left-handed helices [22,42–44], implying that introduction of optically active additives to the radical polymerization could lead to helix-sense selection. Helix-sense selection by radical mechanism has been realized by the polymerization using an optically active initiator, chain-transfer agents, solvents [43,44], or a chiral cobalt complex (**Co(II)-L***) [47]. A completely single-handed helical poly(**PDBSMA**) can be prepared using **Co(II)-L*** under mild reaction conditions. Although it is not completely clear, interaction between the Co(II) complex, a d^7 species, and the growing radical is considered to be responsible for the helix-sense-selection mechanism. It has been proposed that the polymerization of **PDBSMA** proceeds only through right- and left-handed helical radicals and the two radicals have different interactions or binding constants with **Co(II)-L*** (Fig. 5).



Co(II)-L*

Helix-sense selection has been also studied using bulky methacrylates having a chiral side group including **PPyoTMA** [48], **IDPDMA** [49], **2F4F2PyMA** [50], and **TADDOL-MA** [51]. **TADDOL-MA** gives a polymer having cyclic structures in the main-chain by cyclopolymerization. The helical structure of this polymer may be significantly different from the other polymethacrylates based on the main-chain cyclic structure and therefore, the polymer might possibly show completely different chiral recognition ability from that of the other helical polymethacrylates including poly(**TrMA**).



Studies on free-radical helix-sense-selective polymerization is important not only because radical polymerization is cost-efficient but also because it is versatile, that is, a single-handed helical polymer may be obtained by direct radical polymerization of monomers having functional groups which inhibits anionic polymerization. Single-handed helical polymers bearing functional side chains may possibly show completely different molecular recognition ability from those without functional groups.

2.1.2. Chiral recognition

*2.1.2.1. Poly(**TrMA**)*

The helical polymethacrylates show chiral recog-

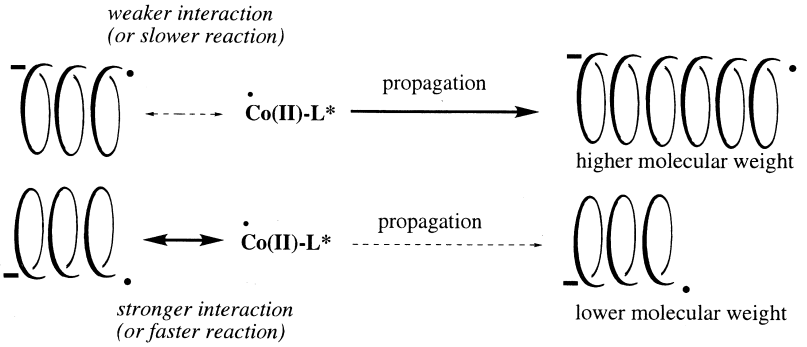
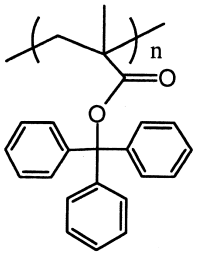


Fig. 5. Mechanism of helix-sense-selection in radical polymerization of **PDBSMA** using **Co(II)-L***.

nition ability towards various types of compounds including macromolecules [13,14,19,20]. Among the polymers, poly(**TrMA**) shows especially high resolving power toward various racemates. This is quite in contrast to the fact that optically active polymethacrylates bearing a chiral side chain which do not possess single-handed helical structure have almost no chiral recognition ability [14]. This supports the assumption that the chiral recognition of poly(**TrMA**) and its analogues is based on the helical chirality.



poly(TrMA)

Resolving power of optically active poly(**TrMA**) was first confirmed using a THF-insoluble (+)-polymer prepared using **Sp**-*n*-BuLi (DP=220) by HPLC or by a simple adsorption method [33,52] and then a soluble polymer with lower DP coated on silica gel was found to exhibit better resolution ability [32]. The insoluble polymer was mechanically ground into fine powder, sieved with a filter to small particles, and then packed into an HPLC column. With this CSP, several stereochemically interesting compounds including Tröger's base, hexahelicene and cyclophanes were effectively resolved. However, because the poly(**TrMA**) particles were brittle, the CSP was not durable enough to be used practically.

A significant improvement not only on durability of the CSP but also on separation ability was made by using macroporous silica gel as a support [32]. The improved CSP was made by coating a soluble poly(**TrMA**) (20 wt%) having a lower DP than that of the insoluble one on silica gel surface. Silica gel (particle size 10 mm, pore size 100 nm) was silanized with dichorodiphenylsilane prior to the polymer coating process. The poly(**TrMA**)-coated silica gel CSP had higher resistance against compression and a longer lifetime than the simply ground poly(**TrMA**) particle. The former CSP had additional advantages over the latter: capacity factors were generally smaller for the former and higher theoretical plates of the packed column were constantly achieved for the former, indicating that the silica-supported CSP allows more efficient and rapid separation.

The silica-supported CSP can resolve more than 200 racemic compounds, some of which are indicated in Figs. 6 and 7 [53–58]. An example of chromatogram is shown in Fig. 8. It is characteristic of the poly(**TrMA**) CSP that it can resolve compounds lacking functional groups whose separation would be difficult by other conventional methods. Resolution with poly(**TrMA**) is best achieved using a polar eluent such as methanol or a methanol–water mixture in most cases, suggesting that resolution takes place through hydrophobic interaction between nonpolar groups of a solute and the side groups (trityl group) of poly(**TrMA**). It has been proposed that the side-chain trityl groups have a chiral propeller structure and it has an important role in chiral recognition [14].

In the resolution using the silica-supported CSP, the ratio of poly(**TrMA**) to silica gel has an influence on the resolution behavior [14]. For example, in the resolution of binaphthol using methanol as a mobile phase, retention volume increased linearly with the poly(**TrMA**)-silica gel ratio in the range of the ratio up to 3/7 (w/w) while in the resolution of the *N,N′*-diphenyl-*trans*-cyclobutane-1,2-dicarboxamide, retention volume had maximum at the ratio of ca. 0.2. These findings may be interpreted in terms of the difference in aggregation state of poly(**TrMA**) chains (Fig. 9). At a high concentration of the polymer, the helical chains will aggregate in an ordered form which may create new chiral spaces between closely packed polymer chains whose shapes may be different from those of the spaces around isolated helical chains. The new chiral spaces may show chiral recognition different from that of the isolated polymer chain. This accounts for the difference in separation ability of CSP's with different polymer–silica ratios and also that between silica-supported CSP and finely ground polymer.

The stereochemistry of polymer–solute interaction has been considered [52]. In the results of resolution of the compounds having a C_2 axis and two aromatic groups shown in Fig. 10 using (+)-poly(**TrMA**),

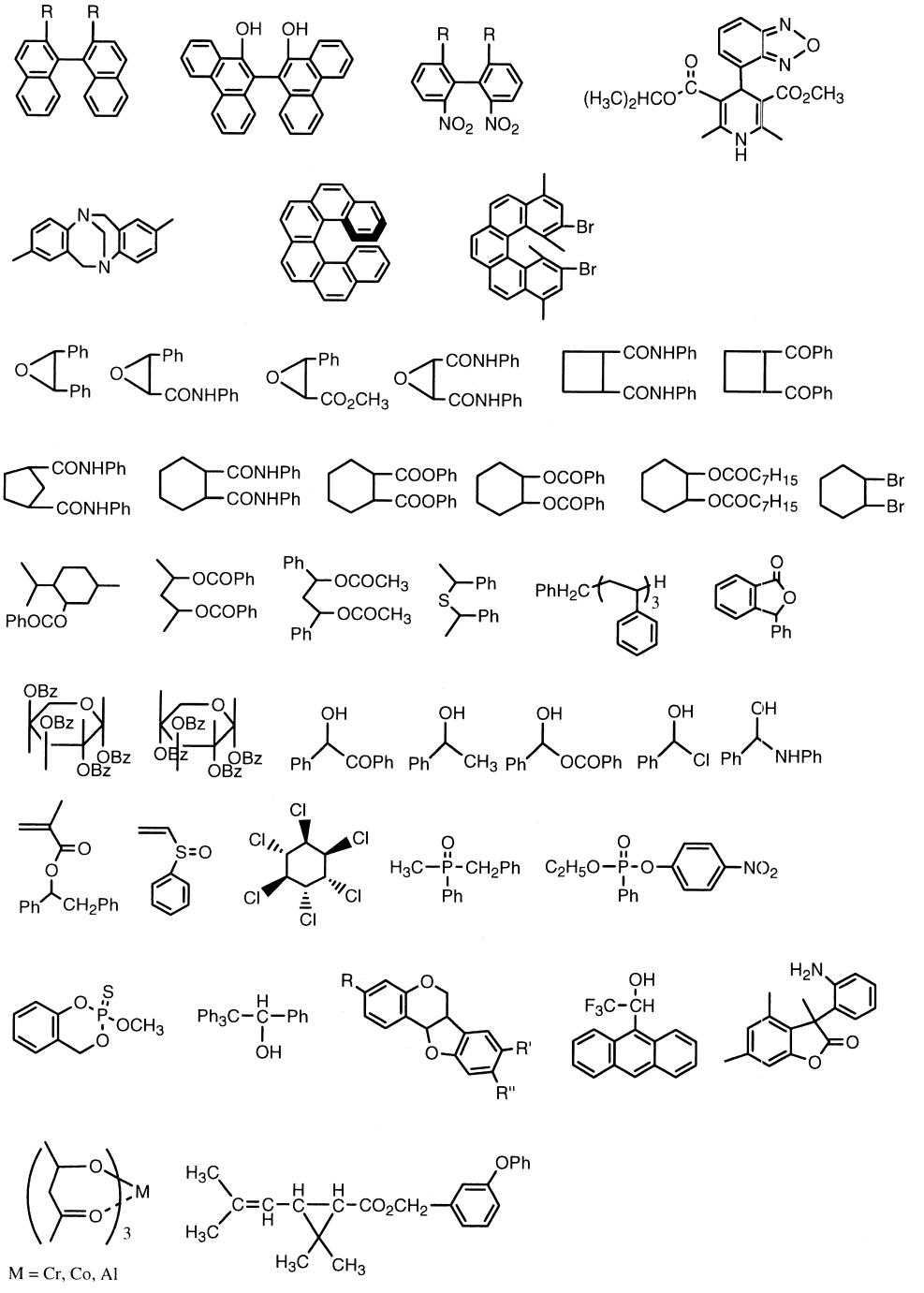


Fig. 6. Compounds resolved on poly(TrMA) (1).

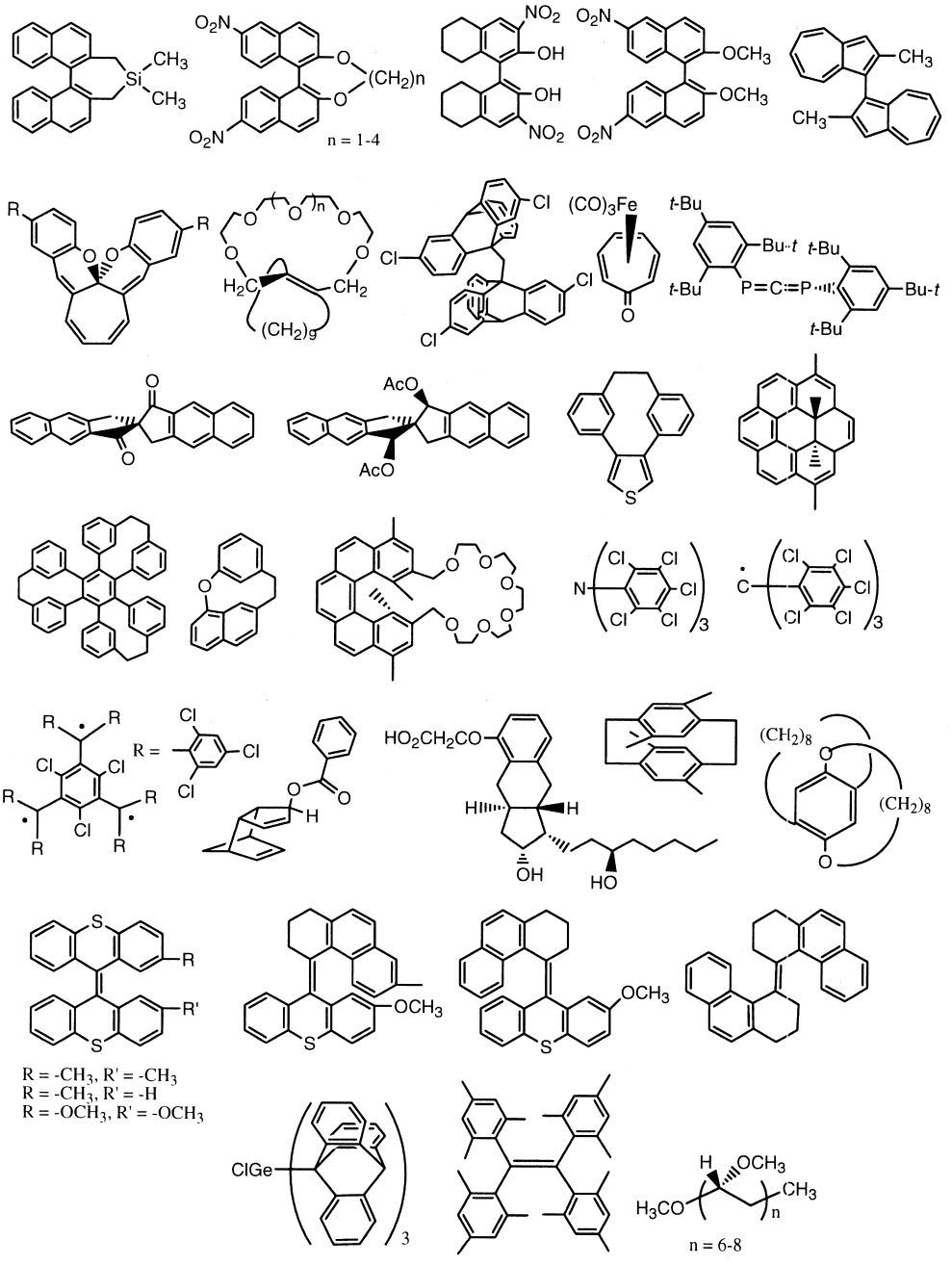


Fig. 7. Compounds resolved on poly(TrMA) (2).

one finds a tendency that more retained enantiomers have P-helicity with respect to their aromatic groups if one looks at the molecule from the direction perpendicular to a C_2 axis. On the basis of this tendency, the (+)-poly(**TrMA**) may have a right-handed helical conformation, and the absolute con-

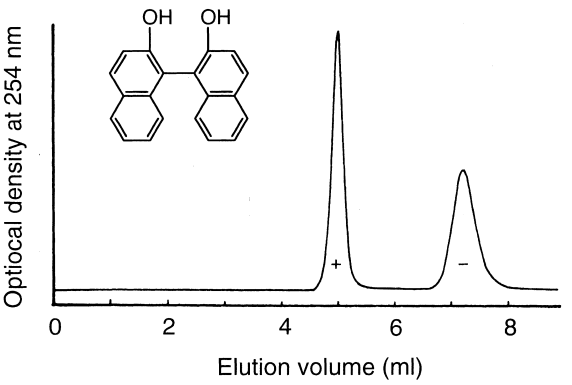


Fig. 8. Resolution of binaphthol on (+)-poly(TrMA)-coated silica gel. Reproduced with permission from J. Am. Chem. Soc., 1981, 103, 6971–6973. [Copyright 1982 Am. Chem. Soc.].

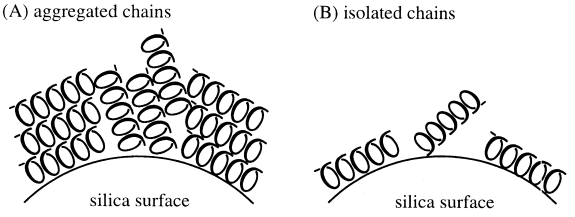


Fig. 9. Suggested difference in the aggregation state of poly-(TrMA) chain on silica surface: aggregated chains at a high poly(TrMA) to silica ratio (A) and isolated chains at a low poly(TrMA) to silica ratio (B).

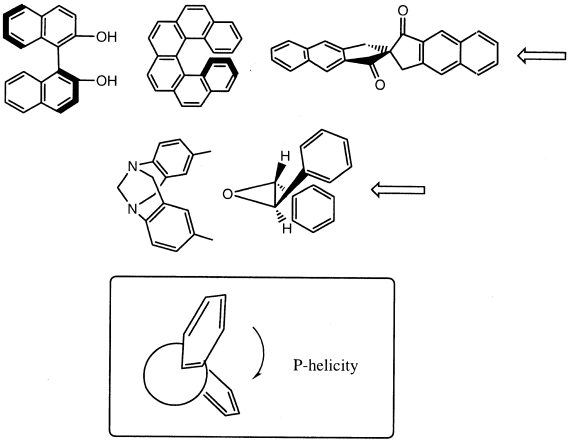


Fig. 10. Antipodes having stronger interaction with (+)-poly-(TrMA). Arrows indicate the direction of C2 axes.

figuration of a compound resolved on poly(**TrMA**) may be predictable if the compound is similar in structure to those in Fig. 10.

A poly(**TrMA**) CSP in which the helical polymer was chemically bonded to silica gel has been also made and evaluated [59]. An advantage of this CSP is that aromatic hydrocarbons, chloroform, and tetrahydrofuran can be used as eluent. These solvents cannot be used for the silica-supported poly(**TrMA**) column because they will wash the helical polymer off the surface of silica gel. The chemical bonding of poly(**TrMA**) with silica gel was achieved by (A) the reaction of a block copolymer of **TrMA** and 3-trimethoxysilylpropyl methacrylate with silica gel or by (B) the reaction of poly(**TrMA**) having a PhNH-CH_2CH_2-N(Ph)- terminal group with silica gel pretreated first with (3-aminopropyl)triethoxysilane and then with toluen-2,4-diyldiisocyanate (Fig. 11). The chiral recognition ability of the chemically bonded CSP was similar to that of the poly(**TrMA**)-coated silica gel when methanol was used as eluent. With the chemically bonded CSP, racemic helical polymers (a equimolar mixture of right- and left-handed helices) are partially resolved into optical isomers. Helical polymers resolved on this CSP include helical (±)-poly(**TrMA**) [59], (±)-poly(**D2PyMA**) [38], and (±)-poly(**PDBSMA**) [43] which are insoluble in methanol. An equimolar mixture of poly((+)-1-phenylethyl methacrylate) and poly((−)-1-phenylethyl methacrylate) has been also resolved [59].

*2.1.2.2. Poly(**D2PyMA**)*

As a helical polymer with improved durability, poly(**D2PyMA**) was designed after poly(**TrMA**). Asymmetric polymerization of **D2PyMA** was described in 2.1.1. As discussed earlier, **D2PyMA** monomer is much more durable against methanolysis than **TrMA** monomer [39]. Durability of optically active poly(**D2PyMA**)-coated silica gel was also confirmed by monitoring the decomposition of the polymer on silica gel soaked in methanol at 60°C: solvolysis of poly(**D2PyMA**)-coated silica gel was 16-fold slower than that of poly(**TrMA**)-coated silica gel under identical reaction conditions [39]. Although the difference in durability was smaller for the CSP than for the monomers, the poly(**D2PyMA**) CSP was indicated to be relatively stable.

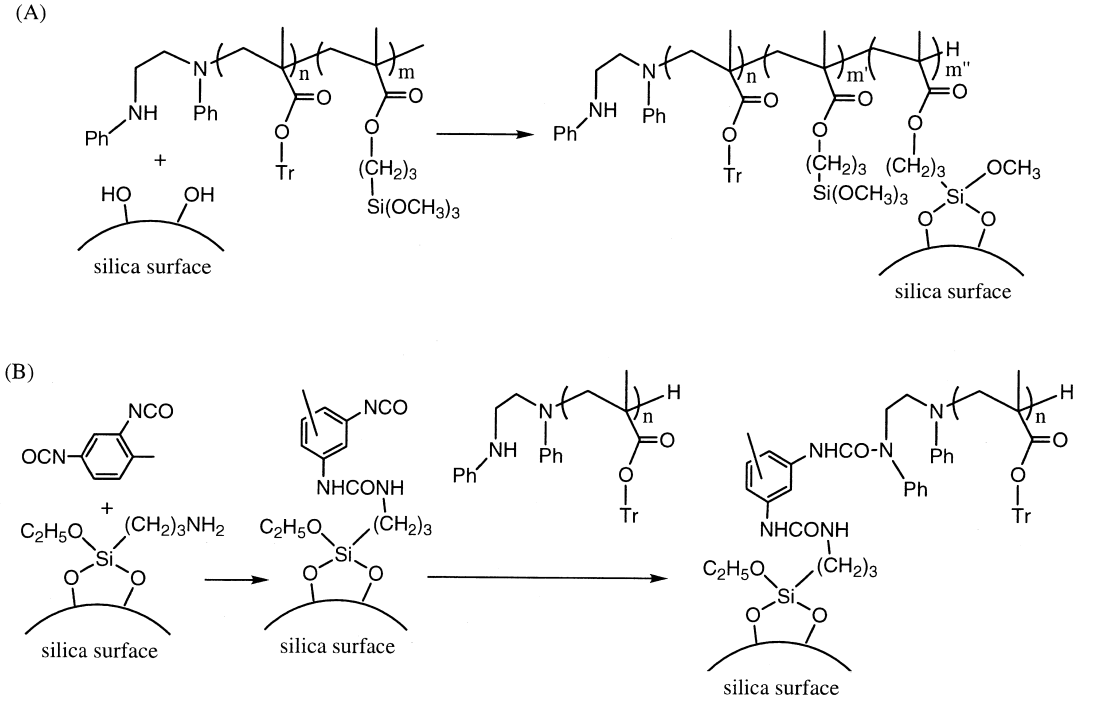
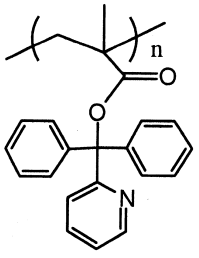


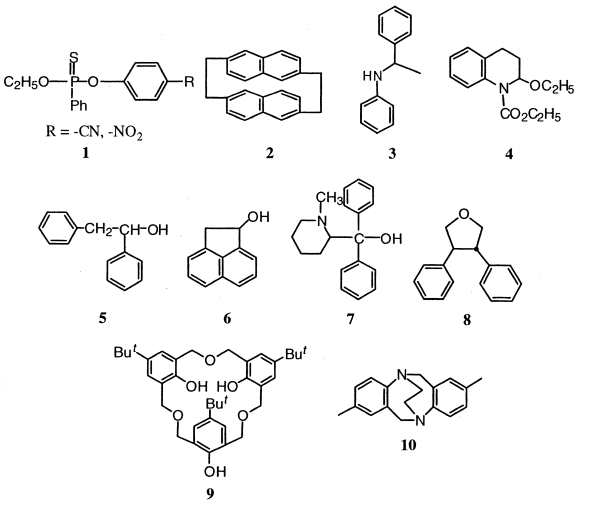
Fig. 11. Preparation of chemically bonded poly(TrMA) CSP.



poly(D2PyMA)

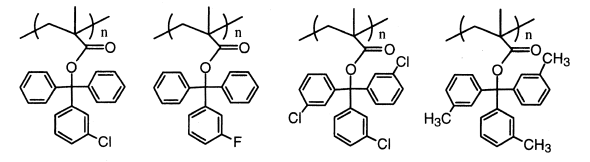
Chiral recognition ability of the poly(**D2PyMA**)-coated silica gel was generally slightly lower than the poly(**TrMA**)-coated silica gel under the same chromatographic conditions using methanol as eluent though the compounds including **1–4** and some binaphthyl derivatives were more efficiently resolved on poly(**D2PyMA**) [39]. In most cases, the poly(**D2PyMA**) CSP separated racemates more effectively using methanol than with non-polar solvents. This indicates that non-polar or hydrophobic interactions between a racemate and the chiral stationary phase is an important factor for chiral discrimination as well as in the case of poly(**TrMA**) CSP. However, resolution of several racemates including $Co(acac)_3$, $Cr(acac)_3$, and **5–8** were better achieved on the poly(**D2PyMA**) CSP with a hexane-2-propanol mixture than with methanol as eluent. Among the compounds, $Co(acac)_3$, $Cr(acac)_3$, **7**, and **8** was not resolved at all when methanol was eluent. An interesting finding regarding this was that **5** and its methyl ether gave similar capacity and separation factors when methanol was used while **5** was more strongly retained and better resolved than the methyl ether when hexane-2-propanol was used. This indicates that the hydroxyl group interacts with the pyridyl group of the polymer side chain through hydrogen-bonding and this polar interaction is important in the separation mechanism.

The poly(**D2PyMA**) CSP can also resolve a calixarene derivative (a pseudo-C2-symmetrical macrocycle) (9) [60] and a Tröger's base analogue (**10**) [61].

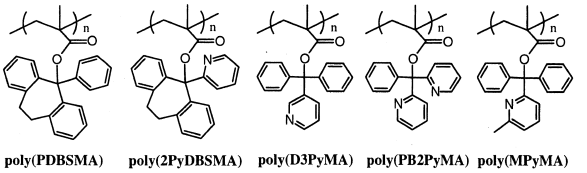


*2.1.2.2.1. Other helical polymethacrylates designed after poly(**TrMA**) and poly(**D2PYMA**).* Chiral recognition ability of several helical polymethacrylates having similar structures to those of poly(**TrMA**) and poly(**D2PyMA**) have been evaluated although some of them were only tested by chiral adsorption experiments.

Four meta-halogen- or meta-methyl-substituted optically active poly(**TrMA**)-derivatives (poly(**m-Cl_1TrMA**), poly(**m-F_1TrMA**), poly(**m-Cl_3TrMA**), and poly(**m-Me_3TrMA**) have been synthesized in a single-handed helical form and coated on macroporous silica gel [34]. Poly(**m-Cl_1TrMA**), poly(**m-F_1TrMA**), and poly(**m-Cl_3TrMA**) showed slightly low chiral recognition ability than poly(**TrMA**) and poly(**m-Me_3TrMA**) had almost no resolving ability. Conformation of the side chain triaryl group and the solute–polymer interaction seem to be affected by the substituent introduced to the phenyl groups.

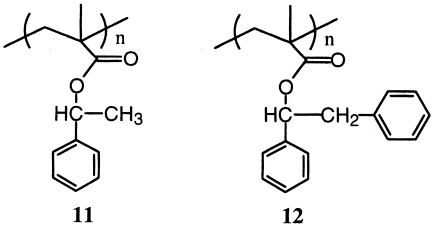


Poly(**PDBSMA**) [46] and poly(**2PyDBSMA**) [45] showed rather low chiral recognition ability. Interaction between the side-chain and a solute may prevent the ethylene group from tying two phenyl groups. Chiral recognition ability of poly(**PB2PyPMA**) [41], poly(**D3PyMA**) [40], and poly(**MPyDMA**) [62] was also lower than that of poly(**TrMA**) or poly(**D2PyMA**).



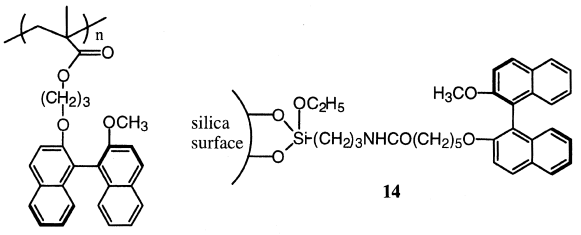
As so far discussed, poly(TrMA) and poly(D2PyMA) showed better resolving power towards many racemic compounds than the other helical polymethacrylates in most cases. However, from the view of practical use of the CSP's, it would be important that various polymers with different resolution characteristics are available and they complement each other. Hence, the design and evaluation of wider variety of helical polymethacrylates is considered to be of importance.

2.1.2.2.2. Other non-helical poly(meth)acrylates. Optically active, the isotactic polymethacrylates, **11** and **12**, prepared from optically active monomers show no chiral recognition to many compounds [14]. These polymers are reasonably assumed not to possess helical conformation, indicating that the single-handed helical conformation is indispensable in the chiral recognition in the examples discussed so far.



An optically active polymethacrylate having binaphthol moiety in the side chain (**13**) has been synthesized by radical polymerization of the corresponding monomer and a CSP was made by coating the polymer onto silica gel [63]. This CSP effectively separated the enantiomers of several racemates including 3,5-dinitrophenylcarbamates derivatives of 1,2- and 1,3-diols and 1-phenylalkanol although the polymer probably does not have a helical conformation. In this case, the resolution seems to be simply

based on the chiral binaphthyl group in the side chain because a CSP prepared by chemically bonding (*S*-)2-(5-carboxypentyloxy)-2′-methoxy-1,1′-binaphthalene (**14**) to an aminopropylsilanized silica gel gave similar results of resolution as those with the polymer.



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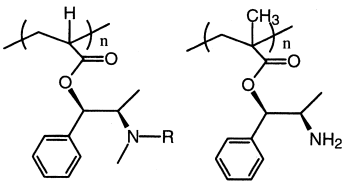
Optically active polyacrylate, **15**, and polymethacrylate, **16**, have been prepared [64]. Polymer **16** was shown to resolve some drugs [65].



15 16

2.2. Polyacrylamides and polymethacrylamides

Successful chiral recognition has been achieved using polyacrylamides and polymethacrylamides bearing a chiral side chain (**17,18**) designed by Blaschke and coworkers [66–68]. The polymers were obtained by free-radical polymerization of the corresponding monomers and the CSP's were prepared by two different methods.

CSP's were first made by free-radical suspension copolymerization of optically active monomers with ethylene diacrylate as a cross-linking agent resulting in gels. The gels swelled in eluents and were used as CSP for low-pressure chromatography and resolved many pharmacological important racemates including drugs in a preparative scale. This work allowed evaluation of the difference of pharmacological behaviors between the enantiomers. For example, the teratogenic effect of thalidomide (**19**) (Fig. 12), whose enantiomers were completely resolved using a Blaschke's CSP (polymer **17**, *R*=methyl, *R′*=cyclohexyl), was found to be caused mainly by (*S*-)isomer [69]. Chiral recognition behavior varied depending on the structure of the polymer and racemate and also on the chromatographic conditions: thalidomide is completely resolved on polymer **18** (*R*=benzyl, *R′*=ethyl) but not on polymer **17** (*R*=cyclohexyl, *R′*=methyl), and mephenytoin (**20**) was sufficiently resolved on the former polymer but only poorly on the latter [67,68]. In the resolution using the polyacrylamides and polymethacrylamides, nonpolar solvents such as benzene and toluene give better resolution results than polar solvents. Also, racemates having functional groups such as amide, imide, carboxylic acid, and alcohol which are capable of hydrogen bonding are resolved well. For instance, mesuximide (**21**) and chlormezanon (**22**) are hardly resolved but their analogs, **20** and **23**, having an amide hydrogen are completely resolved.

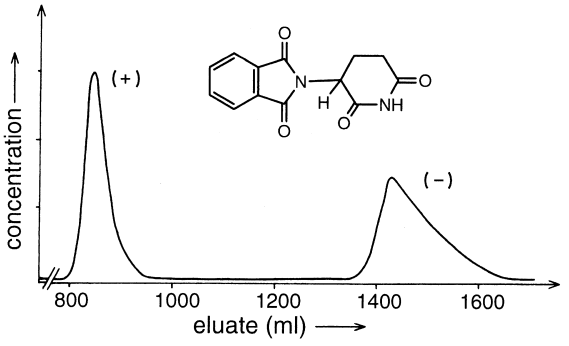
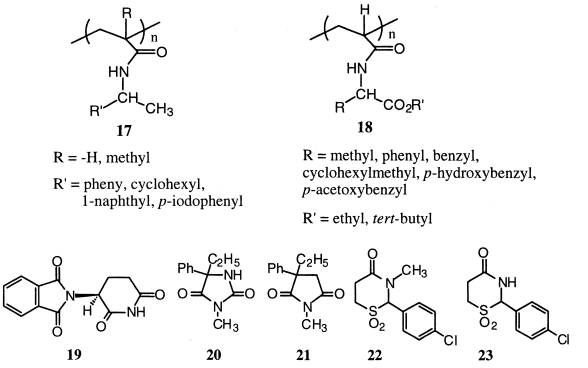


Fig. 12. Resolution of thalidomide on optically active polymethacrylamide (17). Reproduced from J. Liq. Chromatogr., 1986, 9, 341–368. [Copyright 1986 Marcel Dekker].



As compared with the gels described above, gels

prepared by macromolecular reaction between optically active amines and cross-linked poly(acryloyl chloride) showed lower recognition ability [66]. This may be based on some difference in stereostructure (configuration and conformation) of polymer chain or in higher-order structure formed by polymer chains.

In order to make a CSP which can be used for HPLC, polyacrylamide was chemically bonded to a silica gel surface [67]. A methacryloyl or acryloyl group was introduced to a silica gel surface and radical polymerization of an optically active monomer was carried out in the presence of the modified silica gel. By removing unbound polymers by washing with toluene, silica gel bound with chiral polymer was obtained. Immobilization of a polymer on silica gel was also performed by simply polymerizing a chiral monomer in the presence of silica gel. In this case, the polymer was bound to silica gel probably though mechanical tangling of the growing chain in the pores of silica gel and was not removed by washing with hexane, toluene, dioxane, or 2-propanol. The polymer-attached silica gel thus obtained resolved various compounds including those in Fig. 13 when used as CSP for HPLC. Packed columns of polymer **18** (R = benzyl, R' = ethyl) bound to silica has been on the market.

Other than the those discussed so far in this section, poly(meth)acrylamides **24** [70], **25** [71], **26** [72], **27** [73], **28** [64], and **29** [74] have been obtained by radical polymerization of the corresponding monomers and used to make CSP. The CSP of the polymer **24** bonded to silica gel has been commercialized. Uniformly-sized polystyrene beads containing polymer 25 has been obtained by a two-step polymerization technique [71]. This CSP can resolve binaphthol completely. Polymer **28** having ephedrin moiety and polymer **29** can resolve mandelic acid and lysin, respectively. In addition, a

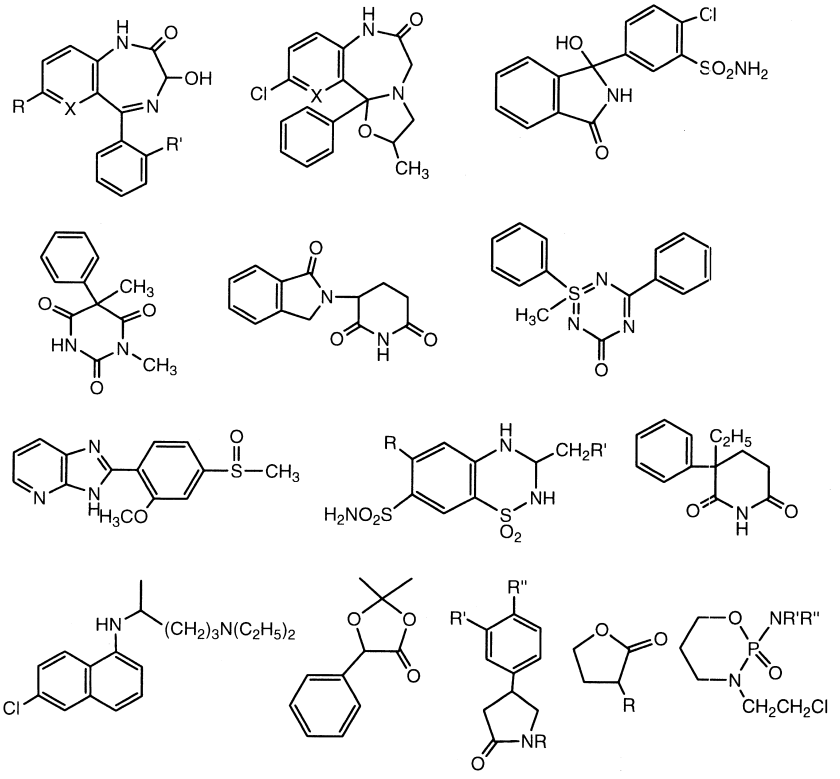
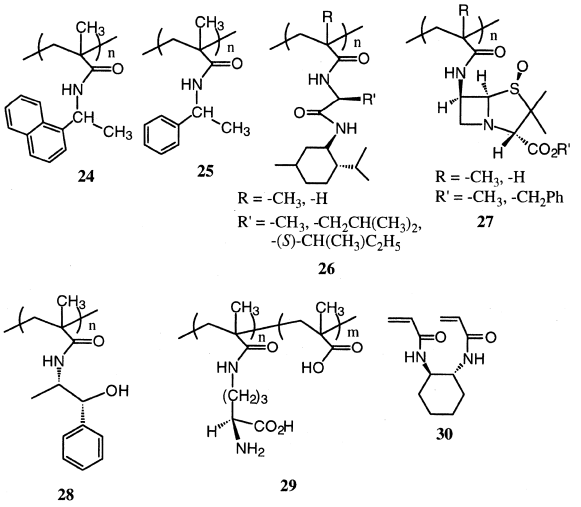


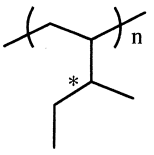
Fig. 13. Compounds resolved on poly(meth)acrylamides.

bifunctional monomer (**30**) was polymerized in the presence of silica gel having –SH groups on the surface to immobilize the obtained polymer [75]. This polymer can resolve binaphthol and its analogues.



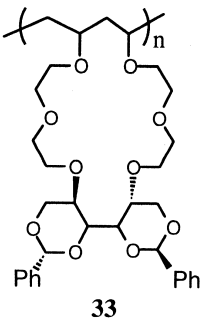
2.3. Polyolefin

An equimolar mixture of poly[(*R*)-4-methyl-1-hexene] and poly[(*S*-4-methyl-1-hexene] were separated into the enantiomeric fractions on crystalline and insoluble (+)-poly[*(S)*-3-methyl-1-pentene] (**31**) [76]. Stereoregular poly(α-olefin)s having optically active side groups are known to assume single-handed helical conformation [8]. Helical conformation of the solute and CSP seem to play a role in the recognition.

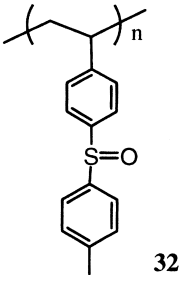


2.4. Polystyrene derivative

An optically active styrene derivative having sulfoxide moiety was prepared and polymerized using α,α′-azobisisobutyronitrile as a radical initiator. The obtained polymer (**32**) was ground to a



powder (mean particle size 7 μm). When the particles were packed in a column and used as CSP of HPLC, several alcohols and amines having aryl group including *o*-(1-methylbenzyl)phenol and α-isopropylbenzylamine were resolved. However, this CSP could not resolve aliphatic alcohols and amines [77].

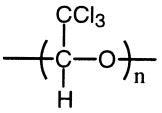


2.5. Poly(vinyl ether)s

Cyclopolymerization of chiral divinyl ethers gives poly(crown ether)s. The polymers show chiral recognition ability toward α-amino acids when they are used as liquid or solid membrane [78,79]. The polymer **33** has been indicated to resolve methyl esters of racemic phenylglycine, valine, and methionine as CSP for column chromatography [80].

2.6. Polychloral

Single-handed helical, optically active polychloral (**34**) is obtained by anionic polymerization of chloral using chiral initiators. The polymer partially resolved isotactic (±)-poly(phenylethyl methacrylate) [81] and *trans*-stilbene oxide [82].



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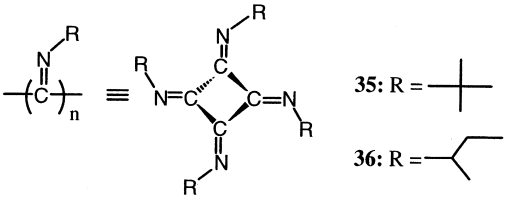
2.7. Polyisocyanide

A mixture of right- and left-handed helical chains of poly(*t*-butyl isocyanide) (**35**) was partially resolved by column chromatography using poly[(−)-*sec*-butyl isocyanide] (**36**) [83]. The recognition may be governed by single-handed helical conformation of the CSP polymer. The same CSP failed in resolving *sec*-butylamine and *sec*-butyl alcohol. However, optically active, single-handed helical poly(*t*-butyl isocyanide) (**35**) synthesized using a chiral catalyst system consisting of $Ni(ClO_4)_2$ and (*R*)-phenylethylamine partially resolved some low-molecular-weight racemates including menthol, $Cr(acac)_3$, $Co(acac)_3$, and binaphthol when coated on silica gel and used as CSP [84].



2.8. Polyacetylene

An optically active polyphenylacetylene derivative (**37**) shows chiral recognition ability [85]. The polymer obtained by polymerization of the corresponding acetylene derivative using a rhodium catalyst had an almost complete *cis*-transoidal conformation and appeared to have a predominant single-handed helical structure. A CSP for HPLC was made by coating this polymer onto a silica gel surface. The CSP resolved several enantiomers including Tröger's base and stilbene oxide. It is interesting that a polymer having the same chemical structure as **37** and much lower stereoregularity prepared independently showed only poor resolving power. This indicates that helical structure plays an important role in the chiral recognition by **37**. Chiral polyacetylene derivatives, **38** and **39**, were also prepared and their chiral recognition ability was investigated [86]. The polymers were immobilized onto silica gel by polymerization in the presence of silica gel bearing chemically bonded phenylacetylene moiety (Fig. 14). A CSP was also made by coating polymer **38** on silica gel. Several racemates including Tröger's base analogues, trans-stilbene oxide, and spiropyran derivatives were resolved on the CSP's. The chiral recognition behavior of chemically bonded **38** and that of coated **38** were rather similar, indicating that **38** may have a similar conformation

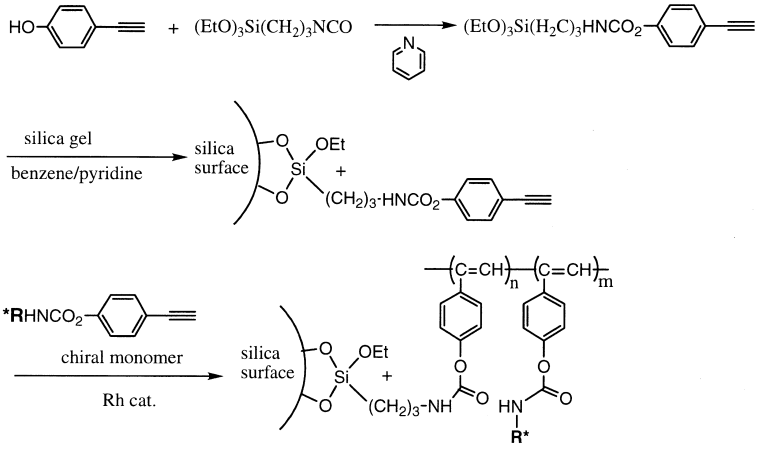
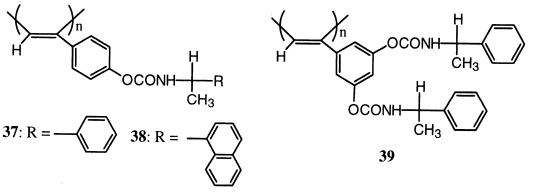


Fig. 14. Immobilization of optically active polyacetylene derivatives on to silica gel.

and make a similar chiral space regardless of the immobilization method. The CSP of polymer **39** chemically bonded to silica gel showed lower resolving power compared with the other CSP's.

Chiral recognition ability of other polyacetylene derivatives have been studied as membrane [87,88].



2.9. Polyether

Anionic cyclopolymerization of **40** gives a polysaccharide-like polyether (**41**) (Fig. 15). The polymer was chemically bonded to silica gel to make CSP. The CSP resolved several racemates including DL-tryptophan and other unprotected α-amino acids [89]. Chiral recognition ability of **41**-analogues has been evaluated [90].

3. Condensation Polymers

Several polyamides and polyurethanes have been prepared from optically active components in search of a good polymer CSP. The polymers show different chiral recognition from those of the addition polymers so far described.

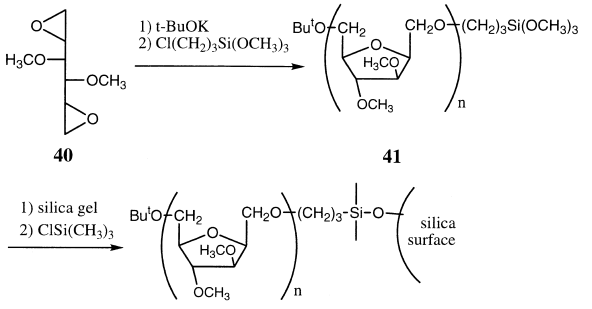
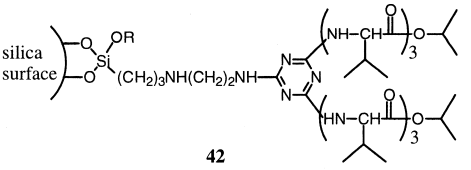
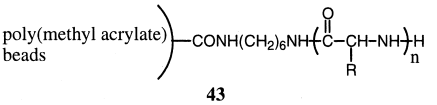


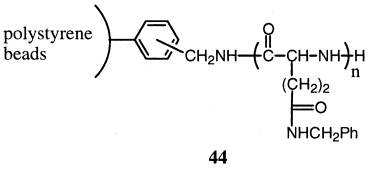
Fig. 15. Cyclopolymerization of a diepoxy-monomer and chemical bonding of the resulting polymer to silica gel surface.

3.1. Polyamides

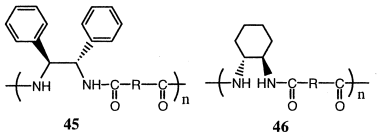
Polymers consisting of α-amino acids (polypeptides) have been reported to show chiral recognition ability. Silica gel-supported *s*-triazine derivative of L-valine isopropyl ester (**42**) showed enantioselectivity towards amino acid derivatives [91]. Some amino acid derivatives were resolved on CSP's containing poly(L-leucine) or poly(L-phenylalanine) chemically bonded to poly(methyl acrylate) macroporous beads (**43**) or spheres consisting of the polypeptide chains themselves [92]. Poly(*N*-benzylglutamine) chemically bonded to polystyrene beads (**44**) also resolved mandelic acid and hydantoin derivatives [93]. Proteins and enzymes are also known to exhibit chiral discrimination of enantiomers and CSP's have been made based on some of them [94–97]. The recognition ability of the fully synthetic polypeptide CSP's seem to be lower that that of the protein based CSP's.







Polyamides prepared from chiral diamine or chiral dicarboxylic acids (or esters) (**45** [98], **46** [99], **47** [100–102], **48** [100], **49** [100], **50** [100], **51** [103], and **52** [99]) can resolve some polar racemates having functional groups capable of hydrogen bonding. The chiral recognition ability depended on the structures of the chiral units and the groups biding the chiral units. For example, polyamides (**47**) having methylene groups of even number in the diamine units show high recognition ability but those of odd numbers do not. This has been ascribed to the



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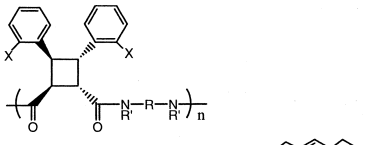
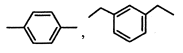
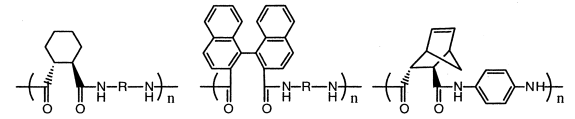


R = -(CH$_2$)$_{2\text{-}10}$-, 
R' = -H, -CH$_3$

47: X = -OH
48: X = -OCH$_3$
49: X = -OCONHPh, -OCONHCH$_2$CH$_2$CH$_3$



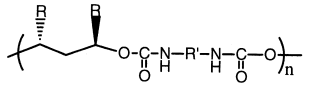
R = -(CH$_2$)$_{3\text{-}8}$-, 

50 51 52

difference of crystallizability of polymers which depends on the number of methylene groups: chiral recognition ability was higher for a polymer with higher crystallizability.

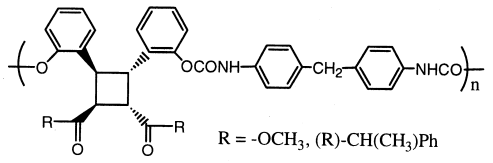
3.2. Polyurethanes

Chiral recognition ability of polyurethanes and poly(urea-urethane) (**53** [104], **54** [105], and **55** [106]) has also been evaluated.



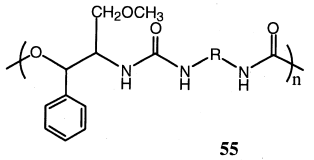
R = -CH$_3$, -Ph
R' = -(CH$_2$)$_{2\text{-}8}$-, 

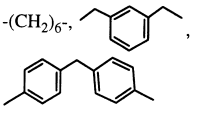
53



R = -OCH$_3$, (R)-CH(CH$_3$)Ph

54



R = -(CH$_2$)$_6$-, 

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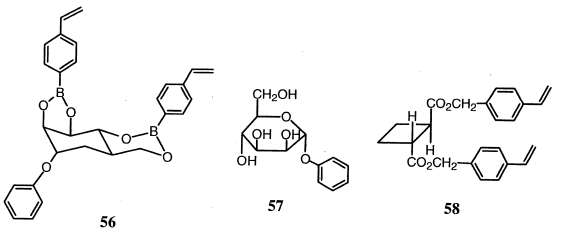
4. Cross-linked gels (Template polymerization)

Cross-linked polymer gels possessing chiral cavities have been prepared and their chiral recognition ability has been studied [5,107–109]. The synthesis of gels is based on molecular imprinting technique. Two distinctive methods have been independently developed, that is, (1) polymerizing a monomer having a removable chiral template moiety with a cross-linking agent and removing the template groups from the products or (2) polymerizing a monomer with a cross-linking agent in the presence of a non-polymerizable template molecule and removing the template. In either way, CSP's having chiral recognition ability are obtained. The former method developed by Wulff and co-workers employs, for example, **56** as a template monomer and ethylene dimethacrylate as a cross-linker [5,107]. An α-D-mannopyranoside derivative (**57**), the template moiety, is split off by hydrolysis with H_2O or methanol. The resulting gel can resolve racemic template. Wulff found that the recognition ability of the gel is significantly affected by the kind and amount of cross-linker agent [110]. A template monomer (**58**) based on *trans*-cyclobutane-1,2-dicarboxylic acid was synthesized by Shea and co-workers [111,112]. The gel obtained using **58** was used as a catalyst for enantioselective reaction. The latter method invented by Mosbach and co-workers employs methacrylic acid as a monomer, ethylene dimethacrylate as a cross-linker, and amino acid derivatives as templates [113–116]. Some amino acid derivatives and β-blockers besides the templates are resolved using the obtained gel. Thimolol (**59**) was completely resolved for the first time using this type of gel without making a derivative [115]. Resolution of Naproxen has also been achieved [116]. An improved separation of Naproxen using uniformly-sized imprint gel made by imprint technique [117]. Molecular imprinting using racemic templates is also known: chiral recognition ability of a chiral gel based on a chiral monomer, (*S*-*N*-methacryloy-1-naphthylethylamine, was enhanced when the gel is prepared in the presence of racemic *N*-(3,5-dinitrobenzoyl)-α-methylbenzylamine [118].

A packed column is obtained without the need of a packing process by performing the imprint polymerization leading to chiral gel directly in an HPLC column. Packed columns obtained this way have



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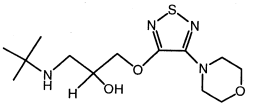

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been shown to have chiral recognition ability [119,120].

The molecular imprinting method has been extended for preparation of membrane [121].

5. Conclusions

Various types of optically active synthetic polymers used for CSP were reviewed. Each polymer CSP has its own characteristic feature of chiral recognition. An ideal polymer would be one that can resolve everything as CSP but such a polymer does not exist in reality though some of the polymers discussed here including poly(TrMA) show resolving ability towards a rather wide range of racemates. A realistic compromise for many scientists who need to separate enantiomers at least on an analytical scale is that they purchase several different CSP's (or packed columns) which work in a complementary manner to cover the necessary range of compounds to be analyzed. Hence, devising both polymers having a wider range of suitable compounds and those having higher separation ability for a specific group of racemates than the existing polymers is considered to be important in this field aside from the efforts to improve separation efficiency of chromatography in general in the field of chemical engineering. Insight into the higher-order structure of polymers on the surface of CSP's and the interaction between the polymers and racemates (molecular recognition mechanism) would help devising new polymers for CSP though such information has been obtained in only limited examples so far including those for polysaccharide derivatives.

From a view of synthetic polymer chemistry, devising a stereoregulation method for polymerization reactions may possibly contribute to invention of a new polymer CSP because stereoregularity of a polymer chain often significantly affects its physical properties in the solid state. Many of the addition polymers reviewed here are prepared by free-radical polymerization, which is versatile and inexpensive but generally poor in control. Applying different polymerization catalyses or stereocontrolled free-radical methods, which is being actively studied recently, may alter the main-chain stereochemistry and also the higher-order structure of the polymer, and therefore may improve the polymers' chiral recognition ability.

Acknowledgements

The author thanks Prof. Eiji Yashima (Nagoya University) for reviewing the draft of the article prior to submission and suggesting relatively new, important literature which the author had been unaware of, and also for fruitful discussions. Prof. Bezhan Chankvetadze, the guest editor of this issue of the journal, is acknowledged for inviting the author to contribute the article. The author is indebted to Prof. Yoshio Okamoto for his continuing mentorship and support for the author since he joined the Okamoto school in 1985. A part of this work was financially supported by NEDO under the Ministry of International Trade and Industry (MITI), Japan and by the Ministry of Education, Science, Sports, and Culture, Japan.

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