Review

Precision synthesis, structure and function of helical polymers

By Yoshio OKAMOTO*1,†

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Abstract: Helical structures are chiral, which means that if we can synthesize a polymer having a stable one-handed helicity, the polymer is optically active. In 1979, we succeeded in the synthesis of a one-handed helical polymer from an optically inactive achiral monomer, triphenylmethyl methacrylate (TrMA). This is the first example of the asymmetric synthesis of an optically active one-handed helical polymer. The polymer (PTrMA) exhibited an unexpected high chiral recognition ability and afforded a practically useful chiral stationary phase (CSP) for high-performance liquid chromatography (HPLC) by coating it on silica gel. In addition, we also succeeded in the development of very useful CSPs for HPLC using the phenylcarbamate derivatives of polysaccharides, cellulose and amylose. These CSPs can efficiently resolve a broad range of chiral compounds, and have been used all over the world for separating and analyzing chiral compounds.

Keywords: asymmetric polymerization, helix-sense-selective polymerization, sparteine, chiral recognition, chiral stationary phase, enantioseparation

Introduction

In nature, chirality (handedness) is one of the basic elements, and life phenomena are inseparable from the chirality of molecules. Biopolymers responsible for vital activity, such as DNA, proteins and polysaccharides, consist of small chiral molecules, sugars and amino acids, and take the left- or right-handed helical structure originating from homochirality of the small molecules. Therefore, the helical structure is the most important and attractive shape of polymers. Since the helical shape itself is chiral, if we can synthesize a polymer with a stable one-handed helical structure from an optically inactive achiral monomer, the polymer must be optically active. This type of polymerization has been called the helix-sense-selective polymerization.

In the 1950s, the historical achievements, which were subsequently awarded with the Nobel Prize, were reported concerning the helical structures of three different types of polymers, protein in 1951,1) DNA in 19532) and isotactic polypropylene in 1955.3) The first two natural polymers have a one-handed helical structure due to the homochirality of amino acids and sugar units, respectively, while the totally synthetic polymer, isotactic polypropylene, consists of equal amounts of right- and left-handed helices and optically inactive. For most naturally-occurring polymers, helical structures are essential for exerting their sophisticated functions in nature. Based on this information, many attempts have been carried out to synthesize optically active polymers with a stable one-handed helicity from optically inactive achiral monomers, such as styrene and methyl methacrylate.4)–8) However, all the attempts failed, because these polymers with rather small side chains are very dynamic in solution and cannot stably maintain their helical structures in solution, even if of polymers. Since the helical shape itself is chiral, if we can synthesize a polymer with a stable one-handed helical structure from an optically inactive achiral monomer, the polymer must be optically active. This type of polymerization has been called the helix-sense-selective polymerization.

Abbreviations: TrMA: triphenylmethyl methacrylate; PTrMA: poly(triphenylmethyl methacrylate); CSP: chiral stationary phase; HPLC: high-performance liquid chromatography; (-)-Sp: (-)-sparteine; BuLi: n-butyllithium; THF: tetrahydrofuran; DDB: 2,3-dimethoxy-1,4-bis(N,N-dimethylamino)butane; DP: degree of polymerization; D2PyMA: diphenyl(2-pyridyl)methyl methacrylate; PMP: ((S)-(+)-2-(1-pyrrolidinylmethyl)pyrrolidine; MCT: microcrystalline cellulose triacetate; CTPC: cellulose trisbenzylcarbamate; CDMPC: cellulose tris(3,5-dimethylphenylcarbamate); ADMPC: amylose tris(3,5-dimethylphenylcarbamate); CBzC: cellulose trisbenzylcarbamate; ABzC: amylose trisbenzylcarbamate; DMA: N,N-dimethylacetamide; SMB: simulated-moving bed; SFC: supercritical fluid chromatography.

*1 Graduate School of Engineering, Nagoya University, Nagoya, Japan.
† Correspondence should be addressed: Y. Okamoto, Graduate School of Engineering, Nagoya University, Furo-cho, Chikusa-ku, Nagoya 464-8603, Japan (e-mail: okamoto@apchem.nagoya-u.ac.jp).

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they are formed by a polymerization process. On the other hand, the monomers with too bulky side chains, like 1,1-diphenylethylene, cannot homopolymerize. These results may indicate that a polymer with a sufficiently stable helicity could be obtained by the helix-sense-selective polymerization of an achiral monomer with suitable bulky side chains.

This review summarizes our achievements over 35 years with respect to the synthesis and chiral recognition of the helical polymers obtained by the helix-sense-selective polymerization of bulky methacrylates and by the modification of polysaccharides, cellulose and amylose.9),10) Asymmetric synthesis of one-handed helical PTrMA

Triphenylmethyl methacrylate (TrMA) is a unique monomer that forms an isotactic polymer, PTrMA, even by a radical process,11) which usually yields atactic or syndiotactic polymers. This unusual feature of TrMA had been considered to be due to the helical conformation of the polymer chain induced by the steric repulsion of the bulky triphenylmethyl groups, although nothing was known about the stability of the helix. Therefore, nobody predicted the formation of a stable helical vinyl homopolymer from an achiral monomer before our discovery of the one-handed helical PTrMA in 1979. In this year, I had an idea that PTrMA may stably exist at a low temperature, like $-78^\circ$C, even though it could be difficult at room temperature. To affirm this possibility, the anionic polymerization of TrMA was carried out with the ($-$)-sparteine-n-butyllithium ($-$)-Sp-BuLi complex at $-78^\circ$C using a quartz vacuum vessel with optical windows, which was placed in a polarimeter for the measurement of optical activity during the polymerization (Fig. 1).12),13) ($-$)-Sp is a commercially-available natural alkaloid, which had been used in 1968 as a chiral ligand in the pioneering research about asymmetric reactions by Nozaki, Aratani and Noyori.14),15) We used ($-$)-Sp as the chiral ligand for the enantiomer-selective polymerization of racemic 1-phenylethyl methacrylate in 1977, and found that a very high enantiomer selection takes place when combined with Grignard reagents.16)–18) The enantioselectivity during the early stage of the polymerization reached 94% enantiomeric excess. This selectivity is even today the highest among the enantiomer-selective polymerizations of racemic vinyl monomers. This finding encouraged us to use ($-$)-Sp as the chiral ligand for the helix-sense-selective polymerization of TrMA.

The ($-$)-Sp-Grignard reagents complex was unable to polymerize TrMA, whereas its BuLi complex polymerized TrMA as shown in Fig. 1.12),13) The polymerization was initiated by adding the toluene solution of the ($-$)-Sp-BuLi complex to the monomer in toluene cooled at $-78^\circ$C. The optical activity of the polymerization system showed no clear change during the initial 1 hr, but gradually increased to reach a rather high constant value, 2.75 degrees, after 12 hr (Fig. 2). This observed value suggested the formation of the one-handed helical polymer with a specific optical rotation $[\alpha]_D = ca. +400^\circ$ or higher at $-78^\circ$C. The polymerization system was then gradually warmed to room temperature to confirm
whether the helical structure is maintained at higher temperatures. The optical activity should significantly decrease, if the helical structure could not be maintained. Interestingly, the optical activity only slightly decreased and remained at a constant value, suggesting the real formation of the polymer with a stable one-handed helicity at room temperature.

PTrMA is readily converted to poly(methacrylic acid) by the treatment with hydrochloric acid in methanol. The poly(methacrylic acid) derived from the above PTrMA with a high optical activity was confirmed to be highly isotactic as expected and completely optically inactive, indicating that the stereoregular polymer could not maintain the helical structure without the bulky triphenylmethyl groups. This experiment is the first asymmetric synthesis of a stable one-handed helical polymer from an optically inactive achiral monomer, and provided clear evidence for the existence of an optically active vinyl polymer with the chirality due only to its helicity. The high molecular-weight PTrMA with a degree of polymerization (DP) above 100 is insoluble in solvents, but the PTrMA with DP = 50 is soluble in solvents, such as tetrahydrofuran (THF) and chloroform. We found that the soluble optically inactive PTrMA produced in THF with BuLi alone without the chiral ligand can be resolved into (+)- and (−)-polymers by column chromatography using the (+)-PTrMA immobilized on silica gel as a chiral stationary phase (CSP). The interaction of the polymer chains with the same helicity is much stronger than that of the opposite helicity. Therefore, the (−)-polymer was eluted much faster than the (+)-polymer by allowing separation of the optically inactive PTrMA. From this study, the highest [α]D of the PTrMA probably having the complete one-handedness was estimated to be around 400°. Therefore, the PTrMA obtained with the (−)-Sp-BuLi must have a high one-handed helicity. We also found that a chiral ligand (S,S)-(+)2,3-dimethoxy-1,4-bis(N,N-dimethylamino)butane DDB (Fig. 3) can more precisely control the one-handedness of PTrMA. Since both (+)- and (−)-DDB are commercially available, we can selectively synthesize the PTrMAs with right- and left-handed helicities using these ligands.

An analogous helical polymer was also obtained from diphenyl(2-pyridyl)methyl methacrylate (D2PyMA). For the helix-sense-selective polymerization of this monomer, (−)-Sp and DDB were not effective chiral ligands always yielding a mixture of right- and left-handed helical polymers. Among the many chiral ligands (Fig. 4) that we examined, only (S)-(+)2-(1-pyrrolidinylmethyl)pyrrolidine (PMP) afforded a polymer (poly(D2PyMA)) with an almost complete one-handedness. Since PMP has a hydrogen on the nitrogen, which can react with a strong base BuLi, we must use a weaker base, such as N,N′-diphenylethenediamine monolithium amide (PhNHCH2CH2N(Ph)Li) or 9-fluorenyllithium, as the initiator. With the PMP initiator system, we could obtain the poly(D2PyMA)s with various DPs. The PTrMA with DP = 50 is conformationally very stable even at rather high temperatures in solution and did not show any change in optical activity when heated at 60°C in THF, and the poly(D2PyMA) with DP = 80 was also conformationally stable mainly due to association of the polymer chains. However, the poly(D2PyMA) with a DP less than 50 was not stable and a significant decrease in optical activity was observed when heated in chloroform at 60°C as shown in Fig. 5. This decrease in optical rotation was associated with the inversion of the polymer chain, because the nearly optically inactive poly(D2PyMA) with DP = 30 isolated after heating at 60°C could be separated into two polymer fractions with high (+)- and (−)-optical activities by HPLC using (+)-PTrMA as a CSP. This means that the poly(D2PyMA) with a low DP always moves between the right- and left-handed helices.

Since we reported the asymmetric synthesis of PTrMA, many analogous polymers with the chirality due to only helicity have been reported as shown in
Fig. 3. Structures of (+)-DDB, (-)-DDB, D2PyMA and PMP.

Fig. 4. Chiral ligands used for the polymerization of D2PyMA with DPEDA-Li and specific optical rotations ($[\alpha]_{D}$) of the obtained polymers.
The existence of the optically active polymer with the chirality arose from only the helicity was found for poly(tert-butyl isocyanide) by Drenth et al. in 1974.26 They succeeded in the separation of the polymer into (+) and (−) fractions by column chromatography using an optically active poly((S)-sec-butyl isocyanide) as a CSP, and in 1988, they reported the asymmetric synthesis of a one-handed helical polymer using a chiral catalyst.27 Most vinyl polymers 1–9, polychloral 10 and polyisocyanide 11 can have stable helical structures at room temperature, while polyisocyanate 12, polycyctene 13, polysilane 14 and polycarbodi-imide 15 have dynamic helical structures, whose helical reversal points can rapidly move along the polymer chains at room temperature.23–25 The studies of helical polymers have significantly expanded in the past 35 years after our discovery of PTrMA.

Chiral recognition of PTrMA and its application for CSP in HPLC

When we obtained the one-handed helical PTrMA, we did not expect a high chiral recognition ability of the PTrMA, because the polymer is almost entirely surrounded by nonpolar triphenylmethyl groups, which cannot strongly interact with many racemates. However, when we checked its chiral recognition ability by a simple experiment, we immediately noticed its high ability, and wanted to use the polymer as the CSP for HPLC. First, the high-molecular-weight insoluble PTrMA was ground to small particles, sieved to 20–50 µm particles, and packed into an HPLC steel column. The packed
column was able to resolve many chiral compounds, particularly stereochemically interesting aromatic compounds.\(^{28,29}\) However, the column was not stable due to the brittleness of the PTrMA particles, which induced clogging of the column bottom filter.

After many trials to overcome this deficiency, we found a simple and good method to prepare a practical and useful CSP for HPLC, as described below. The soluble PTrMA with DP = 50 was coated on commercially-available macroporous silica gels with a particle size of 10 µm and a pore size of 100 or 400 nm. The PTrMA solution in THF was first mixed with the silica gel, then the solvent was evaporated to obtain the PTrMA-coated silica gel, which showed a sufficient stability and efficiency as the CSP for HPLC.\(^{30}\)

Figure 7 shows the HPLC separation of 1,1'-binaphthol using the PTrMA coated on silica gel as a CSP.\(^{30}\) Enantiomers of 1,1'-binaphthol are eluted at t\(_1\) and t\(_2\), and a non-retained compound is eluted at t\(_0\). Based on these values, retention factors k\(_1\) and k\(_2\), and separation factor α are obtained as follows: k\(_1\) = (t\(_1\) - t\(_0\))/t\(_0\) = 0.50, k\(_2\) = (t\(_2\) - t\(_0\))/t\(_0\) = 1.17 and α = k\(_2\)/k\(_1\) = 2.34. Here, the retention factors, k\(_1\) and k\(_2\), indicate the strength of the interactions between the CSP and 1,1'-binaphthol enantiomers, and the separation factor α indicates the chiral recognition ability of a CSP. The α value is correlated to the free energy difference between the interactions of each enantiomer with a CSP by the equation, \(-RT \times \ln α = Δ(ΔG)\). The α value in Fig. 7 is 2.34, and if this value is one, no separation is attained. If this value is 1.2, baseline separation is often expected. In this case, the Δ(ΔG) is −0.11 kcal/mol, indicating that with a small energy difference in chiral recognition, thus a baseline separation can be achieved.

Figure 8 shows the HPLC resolution of 1,1'-binaphthol using the PTrMA coated on silica gel. Column: 0.46 (id) × 25 cm, eluent: methanol, flow rate: 0.5 mL/min. Cited from ref. 30.

A weak point of the PTrMA-based CSP is the fact that the ester bonds of the polymer are rather easily solvolized in methanol to form methacrylic acid residues and methyl triphenylmethyl ether accompanied by a decrease in the chiral recognition ability. Therefore, it was recommended to use the column below room temperature and to completely exchange the methanol with hexane after using the column.

![Fig. 7. HPLC resolution of 1,1'-binaphthol using the PTrMA coated on silica gel. Column: 0.46 (id) × 25 cm, eluent: methanol, flow rate: 0.5 mL/min. Cited from ref. 30.](image)

Fig. 8. Racemic compounds resolved by HPLC using one-handed helical PTrMA.\(^{31}\)
The one-handed helical poly(D2PyMA) exhibited a slightly lower chiral recognition ability than the PTrMA as a CSP for HPLC, but a better resistance against solvolysis by methanol. Its solvolysis rate in methanol was estimated to be about 1/10 that of PTrMA. The PTrMA-based chiral column for HPLC was commercialized in 1982 by Daicel as the first polymer-based chiral column (Chiralpak OT), followed by the poly(D2PyMA)-based column, and the PTrMA column was the second oldest commercialized chiral column.

Development of CSPs based on cellulose and amylose derivatives

During the chiral separation study of the PTrMA, we had the chance to resolve many stereochemically interesting compounds received from many groups all over the world. This experience showed us how the chiral separation by HPLC is valuable and of importance not only for the basic research on chirality, but also for the development of practically useful chiral compounds, such as pharmaceuticals and pesticides, and encouraged us to make further advances using this new chiral separation method.

A polysaccharide cellulose (Fig. 9) is the most abundant polymer on the earth and has a stereo-regular helical structure with a crystallinity. In 1973, Hesse and Hagel reported that the microcrystalline cellulose triacetate (MCT), which was synthesized from crystalline natural cellulose under heterogeneous reaction conditions, exhibits a high chiral recognition to some racemates, particularly aromatic compounds. The MCT has its crystallinity based on the cellulose. Although MCT was an attractive material for chiral separation, its performance was not further improved as a CSP for HPLC. One of the reasons for this difficulty in the improvement is ascribed to the fact that MCT significantly loses its chiral recognition ability when dissolved in a solvent. The high-order structure of MCT that originated from the structure of the native cellulose was completely changed by dissolution. This was already pointed out by Hesse and Hagel, and later when we coated MCT on silica gel, we also observed this phenomenon. Besides MCT, other cellulose derivatives with high chiral recognition abilities were not reported until 1984.

As previously explained, we noticed from the study of the PTrMA that we can readily prepare CSPs for HPLC by coating optically active polymers on silica gel. Actually, in 1984, MCT and cellulose tribenzoate were coated on macroporous silica gel and evaluated as CSPs. These coated-type materials had a much higher performance showing sharper peaks compared to the packing materials derived from the ester alone, and some compounds were resolved with a high selectivity. Besides the esters, the carbamate derivatives of cellulose and amylose were also well-known derivatives of the polysaccharides, while their chiral recognition abilities had not yet been reported. When we evaluated cellulose trisphenylcarbamate (CTPC) as a CSP for HPLC using our coating method, we immediately noticed its very high ability, and many chiral compounds were efficiently resolved. After we discovered this excellent property of CTPC, we learned that Hesse's group also examined the CTPC as a CSP, but did not obtain any significant results. We do not know the reason for this unfavorable result. The purity of their CTPC might be insufficient, because the substitution degree of hydroxyl groups with carbamate groups can clearly influence its ability. The CSPs coated with cellulose tribenzoate and CTPC were commercialized as Chiralcel OB and Chiralcel OC, respectively, by Daicel in 1984. We also evaluated cellulose tribenzoate derivatives with various substituents on the phenyl groups, and found that tris(4-methylbenzoate) showed a much better chiral recognition than...
Table 1. Separation factors (α) for the HPLC enantioseparation of racemates 1–5 using cellulose trisphenylcarbamate (CTPC) derivatives having a substituent at 4-position as CSPs.

| Racemates | CH$_3$OH | C$_2$H$_5$ | CH$_3$ | H- | Br- | Cl- | F- | CF$_3$ | NO$_2$ |
|-----------|----------|-----------|--------|----|-----|-----|----|--------|--------|
| 1         | 1.35(−)  | 1.57(−)  | 1.52(−) | 1.45(−) | 1.29(−) | 1.29(−) | 1.26(−) | 1.30(−) | ~1(+)  |
| 2         | 1.34(+)  | 1.55(+)  | 1.55(+) | 1.46(+) | 1.70(+) | 1.68(+) | 1.38(+) | 1.61(+) | 1.33(+) |
| 3         | ~1(+)    | 1.11(+)  | 1.48(+) | 1.37(+) | 1.19(+) | 1.16(+) | 1.14(+) | 1.25(+) | ~1(−)  |
| 4         | ~1(+)    | 1.76(+)  | 1.75(+) | 1.24(+) | 1.79(+) | 1.46(+) | 1.53(+) | 2.06(+) | ~1(+)  |
| 5         | 1.13(−)  | 1.19(−)  | 1.20(−) | 1.17(−) | 1.17(−) | 1.16(−) | 1.12(−) | 1.18(−) | ~1(−)  |

a) Column: 0.46 (id) × 25 cm, eluent: hexane–2-propanol (90/10), flow rate: 0.5 mL/min. Optical rotation of the first eluted isomer is shown in the parenthesis.

b) Fig. 11.42–46) Almost all kinds of compounds including nonpolar hydrocarbons and polar amines and acids, if they are soluble in hexane-2-propanol mixtures, can be resolved, suggesting that not only polar interactions, such as hydrogen bonds and dipole-dipole interactions, and nonpolar interactions, like the π–π interaction, also play some role in the chiral recognition. The mechanism of the chiral recognition by the CTPC derivatives has been studied in detail by NMR and computer simulation.47)

We also synthesized the phenylcarbamate derivatives of another well-known polysaccharide amylose (Fig. 12), which is different from cellulose in the configuration only at the 1-position, and confirmed that as well CDMPC, amylose 3,5-dimethylphenylcarbamate (ADMC) is an excellent derivative with a high ability.48) The structure (4/3 left-handed helix)49) of ADMPC is quite different from that of CDMPC as shown in Fig. 10. CDMPC and ADMPC show rather complementary chiral recognitions, and with these two derivatives, nearly 80% of 500 racemates have been resolved. CDMPC was commercialized as Chiralcel OD in 1986 and ADMPC as Chiralpak AD in 1987. These two chiral columns have been most frequently used for enantioseparation by HPLC.44–46) The chloro-methylphenylcarbamates, such as the 3-chloro-4-methylphenylcarbamate or 2-chloro-5-methylphenylcarbamate, are also attractive derivatives showing chiral recognitions different from those of the 3,5-dimethyl derivatives.50,51) The regioselective introduction of different carbamate groups at the 2,3-positions and 6-position of the polysaccharides is possible. For instance, 2,3-dio(3,5-dichlorophenyl)-6-(3,5-dimethylphenyl)carba-
mate can be synthesized through the protection and deprotection of the 6-position.\textsuperscript{52,53} These derivatives show a high ability for some racemates.

We also evaluated the chiral recognition abilities of other polysaccharides including chitosan, galactosamine, xylan, dextran, inulin and curdram, as 3,5-dimethylphenylcarbamate and 3,5-chlorophenylcarbamate.\textsuperscript{54} The chiral recognition abilities of these polysaccharide derivatives were generally lower compared to those of CDMPC and ADMPC, although some racemates were better resolved.

Alkyl carbamate derivatives, such as the methyl and propyl carbamates, of cellulose and amyllose show low chiral recognitions as well as benzyl carbamate (CBzC and ABzC, R=H in Fig. 13). However, the derivatives with R=CH\textsubscript{3} or C\textsubscript{2}H\textsubscript{5} have characteristic abilities and some racemates were better resolved on CBzC and ABzC, while the derivatives with R=isopropyl or phenyl show almost no ability.\textsuperscript{55,56} The introduction of the substituent R with an appropriate structure is required to attain a high chiral recognition. The amyllose derivative with R=(S)-CH\textsubscript{3} has been commercialized as Chiralpak AS in 1990.

Immobilization of the polysaccharide derivatives

As already described, the CSPs composed of the polysaccharide derivatives have been prepared by coating the derivatives on silica gel. This means that some solvents, which dissolve or swell the polysaccharide derivatives, cannot be used as the eluents for HPLC. This limitation is a serious drawback of these CSPs, because the selection of a suitable eluent often improves the HPLC separation and the problem of the low solubility of the racemates. The latter is of particular importance for the preparative separation of racemates. To overcome this defect, the polysaccharide derivatives must be immobilized on silica gel.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{structures.png}
\caption{Structures of CTPC, CDMPC and ADMPC. Cited from refs. 40 and 47.}
\end{figure}
without losing their chiral recognition abilities. In 1987, the first immobilization of the CTPC derivatives was performed in my group using diisocyanates which can produce a network between cellulose chains through the formation of two carbamate bonds.\textsuperscript{57} For the efficient immobilization, about 10 mol\% of diisocyanate to the glucose residues had to use. The obtained immobilized CSPs showed slightly lower chiral recognitions compared to those of the coated-type CSPs.

Fig. 11. Compounds resolved on CDMPC.\textsuperscript{42–46}

Fig. 12. Structures of amylose and ADMPC.
Until recently, several immobilization methods have been reported by us and other groups, and the following method (Fig. 14) using a triethoxysilyl group may be one of the most suitable procedures. Cellulose was first dissolved in an N,N-dimethylacetamide (DMA)-LiCl mixture, and then an isocyanate, for instance, 3,5-dimethylphenyl isocyanate (about 60% to total hydroxy groups), was added to convert the hydroxy groups to carbamates and to also eliminate moisture from the reaction system. After this treatment, 3-(triethoxysilyl)propyl isocyanate (2 mol% to the hydroxy groups) was added to quantitatively introduce 3-(triethoxysilyl)propylcarbamate residues to the cellulose, and lastly, an excess of 3,5-dimethylphenyl isocyanate was added to obtain the complete carbamate derivative. Since the triethoxysilyl group is very readily polymerized under acidic conditions, the introduction by only 2% is sufficient for immobilization. More than 90% of the polysaccharide derivative became insoluble through the reaction shown in Fig. 14, and because of the small amount of the 3-(triethoxysilyl)propyl groups, the chiral recognition ability of the derivative is very similar to that of CDMPC. This immobilization method may be applied to all other carbamate and ester derivatives of polysaccharides.

Recently, the immobilized ADMPC, CDMPC and cellulose tris(3,5-dichlorophenylcarbamate) have been commercialized as Chiralpaks IA, IB and IC.
respectively. Using these immobilized CSPs and the prohibited eluents, such as tetrahydrofuran and chloroform, better separations have been attained for many racemates.\(^{58–61}\)

**Methods for the determination of enantiomeric purity**

Before 1981 when we developed the PTyrMA-coated silica gel, most enantiomeric purities of chiral compounds had been estimated on the basis of their optical activities measured by a polarimeter. In order to estimate a reliable purity by this method, the optical rotation of a pure enantiomer must first be known, and a sufficient amount of a pure sample, for instance 20 mg or even more, must be prepared for the polarimetric measurement. These two conditions were often not easy to be filled. On the other hand, a chromatographic method is much simpler, thus we do not need a pure enantiomer and usually less than 1 mg of a sample is sufficient to determine its enantiomeric purity. Figure 15 shows how the enantiomeric purities of chiral compounds were determined in the papers published in the Journal of the American Chemical Society in 2010. In this year, the journal published 3139 papers and 205 papers of them reported the determination of enantiomeric purity. As shown in the left circle, there are four main methods for this determination, i.e., HPLC, GC, supercritical fluid chromatography (SFC) and nuclear magnetic resonance (NMR). The NMR method is becoming less important due to its lower accuracy, and the SFC method can use the same CSPs as in HPLC and is similar to HPLC in property. Middle circle indicates the distribution of the CSPs in the HPLC separation. In most papers, our polysaccharide-based CSPs were used. Molecular-type CSPs are composed of chiral small compounds. The distribution of the polysaccharide-based CSPs is shown in the right circle. OJ and OB are cellulose tris(4-methylbenzoate) and cellulose tribenzoate, respectively, and AS is amylose tris((S)-1-phenylethylcarbamate). IA, IB and IC are the immobilized CSPs of ADMPC, CDMPC and cellulose 3,5-dichlorophenylcarbamate, respectively. In the past 35 years, the determination method of the enantiomeric purity has been completely changed.

**Preparative separation**

The large industrial-scale separation of several chiral pharmaceuticals has been performed using the simulated-moving bed (SMB) system, which has been used for the purification of sugar products. The drugs shown in Fig. 16 have been resolved by the SMB system using the polysaccharide-based CSPs, ADMPC and cellulose tris(4-chlorophenylcarbamate).\(^{63}\) The diameters of the chiral columns are 30–100 cm. For the preparative separation, the loading capacity of the CSPs is an important factor. The coated-type CSPs usually contain about 20 wt% of the polysaccharide derivatives, and the further increase of this content reduces the performance of the CSPs. This defect of the coated-type CSPs can be improved by the hybrid-type CSP prepared by a sol-gel reaction using the polysaccharide derivative containing a small amount of the 3-(triethoxysilyl)-propyl group as shown in Fig. 14.\(^{64}\)
Conclusion

In 1979, we succeeded the first asymmetric synthesis of one-handed helical PTrMA. The obtained polymer exhibited an unexpected high chiral recognition, and the coating of the polymer on silica gel afforded a practically useful CSP for HPLC. With this CSP, many chiral compounds, particularly stereochemically-attractive ones, were resolved. In 1984, we found that cellulose trisphenylcarbamate (CTPC) functions as a very attractive CSP by coating on silica gel. In 1986 and 1987, we developed two very useful CSPs, CDMPC and ADMPC, respectively, which are even today some of the most popular CSPs for both analytical and preparative purposes.

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Profile

Yoshio Okamoto received his B.Sc. (1964) and Ph.D. (1969) from Faculty of Science, Osaka University. In 1969, he joined Faculty of Engineering Science, Osaka University as Assistant Professor and spent 2 years (1970-72) at the University of Michigan with Prof. C. G. Overberger as a postdoctoral fellow. In 1983, he was promoted to Associate Professor, and in 1990 he moved to Nagoya University as Professor. In 2004, he retired from Nagoya University with the title of Professor Emeritus and was appointed as Guest Professor of EcoTopia Science Institute, Nagoya University until 2009. Since 2009, he has been Distinguished Invited University Professor of Nagoya University. He has also been appointed as Chair Professor of Harbin Engineering University in China since 2007. He served as a Research Supervisor of JST-PRESTO “Structure Control and Function” from 2005 to 2011. His research interests include stereocontrol in polymerization reaction, asymmetric polymerization, optically active polymers and enantioseparation by HPLC. He has received Award of the Society of Polymer Science, Japan (1982), Chemical Society of Japan Award for Technical Development (1991), Chemical Society of Japan Award (1999), Molecular Chirality Award (1999), Chirality Medal (2001), the National Medal with Purple Ribbon (2002), Fujihara Prize (2005), Thomson Scientific Research Front Award 2007 (2007), SPSJ Award for Outstanding Achievement in Polymer Science and Technology (2009), and The Ryoji Noyori Prize (2010), Charles G. Overberger International Prize in Polymer Science (2011) and The Japan Academy Prize (2014).