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Enantioseparation on Helical Poly(phenylacetylene)s Bearing Cinchona Alkaloid Pendants as Chiral Stationary Phases for HPLC

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A series of optically active helical poly(phenylacetylene)s bearing cinchona alkaloid pendant groups was coated on macroporous silica gel to obtain novel chiral packing materials for high-performance liquid chromatography, which could resolve diverse racemic compounds into enantiomers whose chiral recognition abilities were significantly influenced by the macromolecular helicity induced by the alkaloid pendants.

Cinchona alkaloids are naturally occurring optically active alkaloids consisting of four pseudoenantiomeric forms (diastereomers), such as cinchonidine (**Cd**)/cinchonine (**Cn**) and quinine (**Qn**)/quinidine (**Qd**) that have been extensively used among the most privileged asymmetric organocatalysts for a broad range of asymmetric reactions.[1] Moreover, cinchona alkaloids, in particular, **Qn** and **Qd** derivatives chemically bonded to silica gel have been reported to show high chiral recognition abilities for acidic racemates under anion-exchange HPLC conditions when used as a chiral stationary phase (CSP), and some of them have been commercialized.[2,3]

Previously, we synthesized a series of optically active, *cis-transoidal* poly(phenylacetylene)s (PPAs) bearing cinchona alkaloid residues as the pendants through an ester (poly-**Cd**, poly-**Cn**, poly-**Qn**, and poly-**Qd**) and amide-linkage (poly-**ACd**, poly-**ACn**, poly-**AQn**, and poly-**AQd**) (Figure 1), which possess a preferred-handed helical conformation induced by the cinchona alkaloid pendants, and catalyzed some asymmetric transformations.[4] Among them, amino-functionalized cinchona alkaloid-bound PPAs were superior to the ester-linked counterparts and efficiently catalyzed the Henry reaction, giving optically active products up to 94% enantiomeric excess (ee) when poly-**AQn** was used as a catalyst whose enantioselectivity was remarkably higher than that catalyzed by the corresponding monomer (28% ee). This noticeable enhancement of the enantioselectivity was ascribed to the induced helical chirality in the polymer backbone because the corresponding nonhelical PPA with the same quinine pendants showed poor enantioselectivity (18% ee).[4b] We anticipated that helical polymers possessing an excellent asymmetric catalytic activity, in particular as an asymmetric organocatalyst might have the potential as a CSP for separating racemic compounds, affording an ideal helical polymer thereby exhibiting enantioselectivities in both the separation of enantiomers and asymmetric transformation of prochiral and/or racemic compounds through organic reactions. However, such examples are quite limited except for a metal-catalyzed asymmetric catalysis using helical poly(diphenyl-2-pyridylmethyl methacrylate) as a polymeric chiral ligand being commercialized as a CSP.[5,6] In this study, the amide-linked cinchona alkaloid-containing PPAs (Figure 1)[4] were coated on silica gel to obtain CSPs for enantioseparation of racemates by

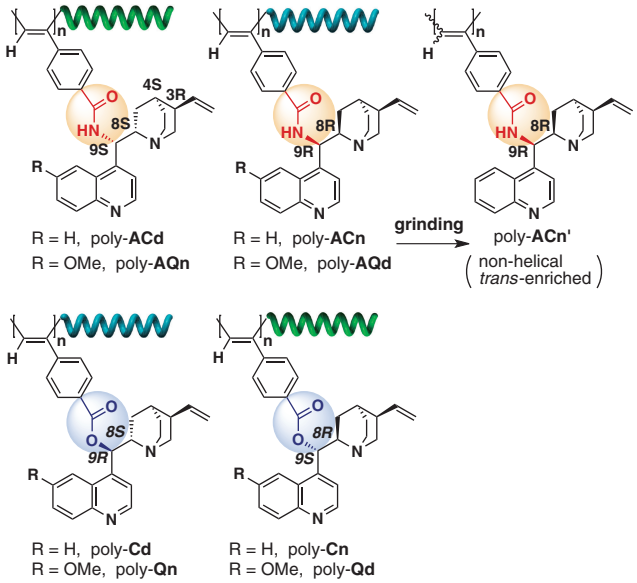


Figure 1. Structures of helical PPAs bearing cinchona alkaloid pendants.

HPLC and their chiral recognition abilities were investigated. For comparison, the corresponding nonhelical amide-linked and helical ester-linked cinchonine-bound PPA-based CSPs were also prepared. We note that CSPs based on cinchona alkaloid-containing helical polymers have not yet been reported.

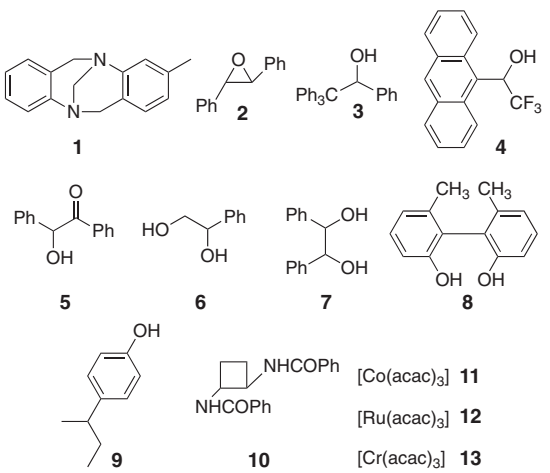
The optically active helical PPAs were prepared according to a previously reported method.[4] The CD spectral patterns between poly-**ACd** and poly-**ACn** (Figure S1A[15]) and also poly-**AQn** and poly-**AQd** (Figure S1B[15]) were almost mirror-images to each other because of their pseudoenantiomeric relationships, suggesting an opposite helical sense induced by the amide-linked cinchona alkaloid pendants.[4b] In addition, the fact that the CD spectral patterns of the amide-linked PPAs were also opposite to those of the corresponding ester-linked PPAs with the same alkaloid moieties suggest that the helical senses of the cinchona alkaloid-bound PPAs are likely determined by the stereogenic centers at the 9-position of the cinchona alkaloids (Figures S1A(b) and S1C(k)).[15]

These helical polymers were then coated on macroporous (3-aminopropyl)triethoxy silanized silica gel (particle size 7 μm, pore size 100 nm) to be used as a coated-type CSP according to a previously reported method,[7] and the obtained packing materials were packed into stainless-steel columns (25 cm × 0.20 cm (i.d.)).[8] The chiral recognition abilities of the helical PPAs coated on silica gel were first investigated by HPLC under the normal-phase condition using hexane–2-propanol (9:1, v/v) as

Table 1. Chromatographic resolution results of racemates on helical PPAs[a]

Racemates	Poly-**ACd**			Poly-**ACn**			Poly-**AQn**			Poly-**AQd**		
	k_1'	a	R_s	k_1'	a	R_s	k_1'	a	R_s	k_1'	a	R_s
1	0.40	1	—	0.37	1	—	0.22	1	—	0.36	1	—
2	0.53	1	—	0.54	1.29 (+)	0.27	0.27	1	—	0.52	1	—
3	3.58	1	—	2.83	1.36 (+)	1.17	1.59	1	—	2.62	1	—
4	12.3	1.11 (−)	0.26	8.41	1	—	5.36	1.24 (−)	0.94	8.70	1	—
5	4.52	1.17 (+)	0.78	3.52	1.19 (−)	1.35	2.45	ca. 1 (+)	—	3.62	1.23 (−)	1.17
6	5.01	1.12 (+)	0.15	4.72	ca. 1 (−)	—	3.48	1.10 (+)	0.44	4.39	1.07 (−)	0.22
7	5.79	1.13 (−)	0.23	6.33	1.44 (+)	1.83	4.36	1	—	6.36	1	—
8	12.3	1.15 (+)	0.42	11.3	1.08 (−)	0.36	5.59	1.19 (+)	0.54	9.36	1	—
9	2.06	1	—	1.89	1.11 (−)	0.33	1.20	1	—	1.65	1	—
10	1.41	1.20 (+)	0.35	1.31	1	—	0.58	1	—	1.05	1	—
11	3.56	1.88 (−)	1.24	3.03	1.67 (+)	1.04	0.85	ca. 1 (−)	—	2.20	3.67 (+)	1.32
12[b]	4.64	2.30 (−)	1.83	3.02	2.81 (+)	2.36	1.26	1.20 (−)	0.24	4.50	ca. 1 (+)	—
13	2.65	2.29 (+)	1.48	1.61	3.02 (−)	2.21	0.77	ca. 1 (+)	—	2.07	3.87 (−)	3.25
Boc-Ala[c]	8.66	1.17 (+)	0.38	6.25	1.13 (−)	0.32	5.99	1.20 (+)	0.45	6.69	1.18 (−)	0.49
Boc-Phe[c]	11.7	1.46 (−)	1.16	9.36	1.15 (+)	0.30	8.31	1.43 (−)	0.85	10.1	1.51 (+)	1.00
Boc-Val[c]	3.82	1.31 (−)	0.78	2.82	1.11 (+)	0.20	2.42	1.14 (−)	0.29	2.78	ca. 1 (+)	—
Boc-Leu[c]	3.77	1.27 (+)	1.03	2.86	1.08 (−)	0.15	2.68	1.10 (+)	0.20	2.82	1.09 (−)	0.10
Boc-Pro[c]	4.99	ca. 1 (+)	—	3.56	ca. 1 (−)	—	3.43	1.42 (+)	1.09	3.56	ca. 1 (−)	—

Racemates	Poly-**Cn**			Poly-**ACn′**		
	k_1'	a	R_s	k_1'	a	R_s
1	0.44	1	—	0.42	1	—
2	0.63	1	—	0.57	1	—
3	4.41	1.49 (−)	1.01	3.84	1	—
4	16.3	1	—	11.6	1	—
5	3.96	1	—	4.53	1.08 (−)	0.30
6	3.67	1	—	5.39	1.06 (−)	0.06
7	5.73	1	—	8.78	1	—
8	11.3	1	—	9.31	1	—
9	1.59	1	—	1.73	1	—
10	0.56	1	—	1.72	1	—
11	0.70	1	—	1.44	1.59 (+)	0.40
12[b]	1.09	1	—	2.08	1.97 (+)	1.16
13	0.70	1	—	1.11	1.89 (−)	0.77
Boc-Ala[c]	7.65	1.10 (−)	0.23	7.26	ca. 1 (−)	—
Boc-Phe[c]	17.5	ca. 1 (+)	—	11.9	ca. 1 (+)	—
Boc-Val[c]	3.98	ca. 1 (+)	—	3.25	ca. 1 (+)	—
Boc-Leu[c]	3.23	ca. 1 (−)	—	3.30	ca. 1 (−)	—
Boc-Pro[c]	4.78	1.49 (−)	0.06	4.14	1	—



[a]*Conditions*: column, 25 × 0.20 (i.d.) cm; eluent, hexane–2-propanol (9:1, v/v); flow rate, 0.1 mL min^{-1}; temperature, 25 °C. The signs in parentheses represent the optical rotation of the first-eluted enantiomers. [b]The signs in parentheses represent the CD detection (254 nm) of the first-eluted enantiomer. [c]Eluent, hexane–2-propanol (9:1, v/v) containing 2% acetic acid.

the eluent, and the chromatographic resolution results for a variety of racemic compounds **1**–**13** are summarized in Table 1 and Figure S2.[15] Figure 2a shows a chromatogram for the resolution of tris(acetylacetonato)cobalt(III) (**11**) on poly-**ACd**. The peaks were detected by a UV detector and identified by a polarimetric detector, and the (−)- and (+)-enantiomers eluted at the retention times of t_1 and t_2, respectively, showing baseline separation. The capacity factor k_1' [$= (t_1 - t_0)/t_0$], the separation factor α [$= (t_2 - t_0)/(t_1 - t_0)$] and the resolution factor R_S [$= 2(t_2 - t_1)/(w_1 + w_2)$] were 3.56, 1.88, and 1.24 respectively (Table 1). Poly-**ACn** also resolved **11** with a good separation factor ($\alpha = 1.67$), but its elution order was reversed (Table 1 and Figure 2b). Similar reversed elution order was observed for other racemates resolved on poly-**ACd** and poly-**ACn** due to their pseudoenantiomeric relationships, although their chiral recognition abilities were more or less different from each other (Table 1). For example, poly-**ACn** partially or completely separated stilbene oxide **2**, a bulky alcohol **3**, and a phenol derivative **9**, which were not resolved at all on poly-**ACd**. In an opposite manner, the latter separated racemic alcohols **4** and **6** and cyclic amide **10**, which were hardly resolved on the former CSP. Poly-**ACd** and poly-**ACn** displayed a higher resolving

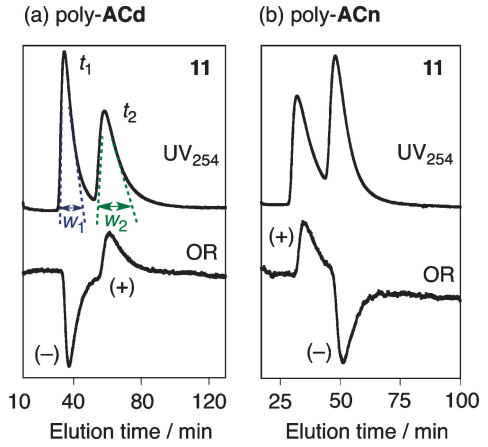


Figure 2. Chromatograms for the resolution of **11** on poly-**ACd** (a) and poly-**ACn** (b). Eluent: hexane–2-propanol (9:1, v/v).

ability than poly-**AQn** and poly-**AQd** did, and could partially or completely resolve nine among thirteen racemates **1**–**13**. Interestingly, poly-**ACd** and poly-**ACn** exhibited excellent chiral recognition abilities toward metal tris(acetylacetonato)s **11**–**13**, giving complete separations with large separation factors, whereas poly-**AQn** and poly-**AQd** only separated four racemates including the metal tris(acetylacetonato)s in a complementary way; the elution orders of enantiomers on poly-**AQn** and poly-**AQd** were identical to those on poly-**ACd** and poly-**ACn**, respectively, indicating that the enantioseparation abilities appear to be fully determined by the helical senses of the PPAs biased by the chirality of the cinchona alkaloid pendants.

On the other hand, the ester-linked cinchonine-bound helical PPA (poly-**Cn**) showed poor chiral recognition ability and resolved only one racemate **3**, indicating an important role of the amide linkages for better enantioseparation.[9] A chiral helical groove with polar amide groups of cinchona alkaloid-bound PPAs exists along the main-chain, which are preferably located inside in a predominant screw-sense via intramolecular hydrogen bonds, resulting from the preferred-handed helical conformations of the polymer backbones, so that polar enantiomers may predominantly interact with the amide residues in the groove through intermolecular hydrogen bond formation. Such helically arranged amide groups of cinchona alkaloid-bound PPAs also contributed to the enantioselective organocatalysis during the asymmetric Henry reaction; poly-**AQn** and poly-**AQd** showed a relatively higher enantioselectivity than those of poly-**ACd** and poly-**ACn**.[4b] However, the chiral resolving abilities of poly-**AQn** and poly-**AQd** as CSPs were lower than those of poly-**ACd** and poly-**ACn**. This may arise from the additional achiral polar methoxy groups attaching to the quinoline rings located away from the helical main-chain, resulting in the decrease of the chiral resolution ability. The importance of the macromolecular helicity on the chiral recognition was supported by the fact that *trans*-enriched poly-**ACn** (poly-**ACn′**) prepared by grinding the *cis*-poly-**ACn** (Figure S1A),[4b,10,15] showed poor chiral recognition ability (Table 1) because the polymer almost lost its helical conformation, resulting in the disappearance of the CD in the polymer backbone regions.

The helical PPAs also resolved the *N*-Boc-amino acids under the anion-exchange condition using hexane–2-propanol (9:1, v/v) containing 2% acetic acid as the eluent (Table 1 and Figure S2).[11,15] Comparison of the resolution results on the CSPs revealed that poly-**AQn** as well as poly-**ACd** showed better chiral resolving abilities among the CSPs and completely or partially resolved all and four *N*-Boc-amino acids, respectively (Table 1). Again, poly-**Cn** and nonhelical poly-**ACn′** exhibited poor chiral recognition.[12,13]

In conclusion, we have found that amide-linked cinchona alkaloid-bound helical PPAs are promising candidates as practically useful CSPs that can efficiently resolve diverse functional racemates including *N*-Boc-amino acids. The importance of the amide-linkage and helical chirality was clearly demonstrated by the facts that the ester-linked cinchona alkaloid-bound helical PPA and amide-linked nonhelical, *trans*-enriched PPA exhibited poor resolving abilities. The present results suggest that helical polymers carrying functional pendants with an asymmetric organocatalytic activity would provide an intriguing scaffold for developing practically versatile chiral materials not only for asymmetric catalysis, but also as CSPs.[14]

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