Chinese Journal of Chemistry, **2004**, *22*, 1070—1074 **Communication**

Enantioseparation of Novel Chiral Tetrahedral Clusters on an Amylose Tris-(3,5-dimethylphenylcarbamate) Chiral Stationary Phase by Normal Phase HPLC

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Amylose tris(3,5-dimethylphenylcarbamate) (ADMPC) coated on a kind of small particle silica gel was prepared. On this ADMPC chiral stationary phase (CSP), the direct enantiomeric separation of six novel chiral transition metal tetrahedral clusters has firstly been achieved using *n*-hexane as the mobile phase containing various alcohols as modifiers. The effect of mobile phase modifiers and the structural variation of the solutes on their retention factors (k') and resolutions (Rs) were investigated. The result suggests that not only the structure and concentration of alcohol in mobile phase, but also the structural differences in racemates can have a pronounced effect on enantiomeric separation. ADMPC-CSP is a suitable CSP for the optical resolution of chiral tetrahedral cluster by HPLC.

Keywords enantiomeric separation, HPLC, chiral stationary phase, amylose tris(3,5-dimethylphenylcarbamate), chiral tetrahedral cluster

Introduction

In recent years, chiral transition metal cluster has attracted a great deal of interests due to its potential application in asymmetric catalytic reaction.[1-3] Producing catalysis for asymmetric induction using a rigid chiral framework would not only bring a basically conceptual breakthrough in the asymmetric catalysis, but also enrich the methodology in the design of new chiral catalysts.[4] So far, a lot of chiral clusters have been reported,[5-9] but only a few of them have been separated into pure enantiomers.[2,10] In general, those racemates of chiral metal tetrahedral clusters obtained from chemical synthesis can not be directly used in asymmetric catalytic reaction. The traditional method for enantioseparation was to convert the chiral clusters into diastereoisomers firstly and then to separate the diastereoisomers by column chromatography. Vahrenkamp *et al.*[2] reported that optically active phosphine ligand can take the place of the carbonyl bound to transition metal to form cluster diastereoisomers, but, in some cases, the auxiliary phosphine can not be removed without destruction of the cluster. The optical activity was otherwise lost after separation of diastereoisomers when phos- phine was removed. Therefore, the preparative enantioseparation of chiral clusters is still a major problem to be urgently resolved in asymmetric catalysis.

Enantioseparation by liquid chromatography on a chiral stationary phase has become an increasingly practical and effective method to obtain optical isomers and determine purity. The method was often used in medicine, pesticides and asymmetric catalysis. A lot of chiral stationary phases (CSP) have been synthesized, of which the phenylcarbamates and esters of polysaccharides, such as cellulose and amylose, exhibited the most universal chiral recognition ability to be available for enantioseparations in HPLC.[11,12] If enantiomers of racemic clusters can be separated directly by HPLC without derivatization, it can be free of the destruction. So, we utilized the modern chromatographic technique for obtaining enantiomer of racemoid clusters.[13] Our group has been engaged in the research for the resolution of enantiomers, including chiral organometallic compounds and so on. Although some of chiral clusters have been discriminated by an amylose tris-(phenylcarbamate) or a cellulose tris-(3,5-dimethylphenylcarbamate),[14,15] some resolutions are too small to be used for their enantiopreparation. So, it is a great necessity for exploring the method used in the resolution of compounds. Recently, we found that the amylose tris-(3,5-dimethylphenylcarbamate) chiral stationary phase (ADMPC-CSP) was effective for the resolution of chiral clusters.

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In this paper, we reported that the enantiomeric separation of six novel chiral transition-metal tetrahedral clusters was achieved on ADMPC-CSP, and the effect of mobile phase modifiers and the structure of chiral tetrahedral clusters on enantioseparation and retention was also investigated. To the best of our knowledge, this is the first report on a direct enantioseparation of these chiral transition-metal tetrahedral clusters using ADMPC-CSP.

Experimental

Chemicals and reagents

Spherical silica gel used in the paper was prepared in our laboratory and had the following properties: particle size, 5 μm; pore size, 13 nm; surface area, 110 $m^2 \cdot g^{-1}$. 3,5-Dimethylphenylisocyanate and amylose were purchased from ACROS (New Jersey, USA). The synthesis of ADMPC was similar to that described in reference.[16] In brief, amylose and 3,5-dimethylphenylisocyanate was refluxed in pyridine to form ADMPC, and then the product was coated on 3-aminopropyl silica gel to form ADMPC-CSP. All other reagents were purchased from Tianjin Second Chemicals reagent plant (China), usually with analytical grade. Six novel chiral transition metal tetrahedral clusters[17] used in the experiment were obtained from the State Key Laboratory for Oxo Synthesis and Selective Oxidation, Lanzhou Institute of Chemical Physics, Chinese Academy of Sciences.

Chromatographic procedure

Chromatographic system consisted of a Waters 515 HPLC pump, a Rheodyne 7125 injector with 20 μL sample loop, and a Waters 2487 double λ absorbance detector (Waters, USA). The chromatographic data were acquired and processed by the Millennium[32] chromatography manager software (Waters, USA). The ADMPC-CSP was packed into a stainless steel column (250 mm×4.6 mm i.d.) by the conventional high pressure slurry-packing procedure.

The mobile phase composition was *n*-hexane with different percentage of various alcohols. Samples were dissolved in mobile phase. All solvents were filtered and degassed in an ultrasonic bath prior to use. The flow-rate was 1.00 $mL \cdot min^{-1}$. The column temperature was 20 ℃. UV detection was performed at 254 nm. The void volume was determined using 1,3,5-tri-*tert*-butylbenzene.

Results and discussion

The structures of the six pairs to be structurally related enantiomer clusters are illustrated in Figure 1, and the crystalline structure of chiral cluster **1** is in Figure 2. Judging from those structures shown in Figure 1, it can be found that the chirality of transition metal tetrahedral clusters is different from that of the customary chiral organic molecules. There are no distinct monoatomic chiral centers, and the chirality results from the general asymmetry of the tetrahedral framework.

Retention factors of the first-eluted peaks, separation factors, and resolutions on ADMPC-CSP column using 2-propanol with different concentration or other alcohols as modifier, are given in Tables 1 and 2. Optimal chromatograms of chiral transition metal tetrahedral clusters **1**—**6**, are shown in Figure 3, respectively.

Influence of modifier concentration

According to the data listed in Table 1, it can be seen that retention factors were evidently changed with increasing the 2-propanol concentration in mobile phase, while separation factors and resolutions varied only a little. Cluster **1** could be separated to baseline under the three chromatographic conditions, whereas cluster **6** could not. The decrease of alcohol concentration in mobile phase resulted in the increase of *R*s, however the band broadening become serious in some cases.

Influence of modifier structure

The effect of the structure of the mobile phase modifiers on retention factors (*k′*), separation factors (α) and resolutions (*R*s) was investigated using a series of alcohols as mobile phase modifiers, and the results are presented in Table 2. It could be observed that the retention of clusters was changed with different modifiers in mobile phase and resolution was also changed to a certain extent. Retention factors and resolutions of the racemates **1** and **2** were decreased with increasing the chain length of the alcohol (ethanol to 1-butanol) used as mobile phase modifier, and the best resolution was achieved by use of ethanol. However, the clusters **5** and **6** were hardly resolved by ethanol/*n*-hexane. All six chiral clusters **1**—**6** could be discriminated with 1-propanol/*n*-hexane. For clusters **1**—**5**, the resolution was different for 1-butanol, 2-propanol and *tert*-butanol as modifiers in the mobile phases, and *tert*-butanol led to the worst separation. These results indicated that the steric bulk and polarity of the alcohol might play a part role in enantiomeric separations of racemic clusters.

A possible explanation for these phenomena was that there was a competition binding to the CSP between alcohol and solute. Different alcohols in mobile phase have different abilities to associate with CSP and modify the steric environment of the chiral cavities of the CSP when binding to achiral sites near the chiral cavities. If the alcohol match with the CSP more strongly, the retention of solute will decrease more seriously while it is used as mobile phase modifier. At the same time, when enantiomers were to enter the chiral cavities, whose steric environment was modified by an alcohol bound with the CSP, thus different enantioselectivity occurred owing to the difference in their steric fit to the chiral cavities of ADMPC-CSP. Figure 3 gave the chromatograms of chiral clusters **1**—**6** in different alcohol as mobile phase modifiers, respectively.

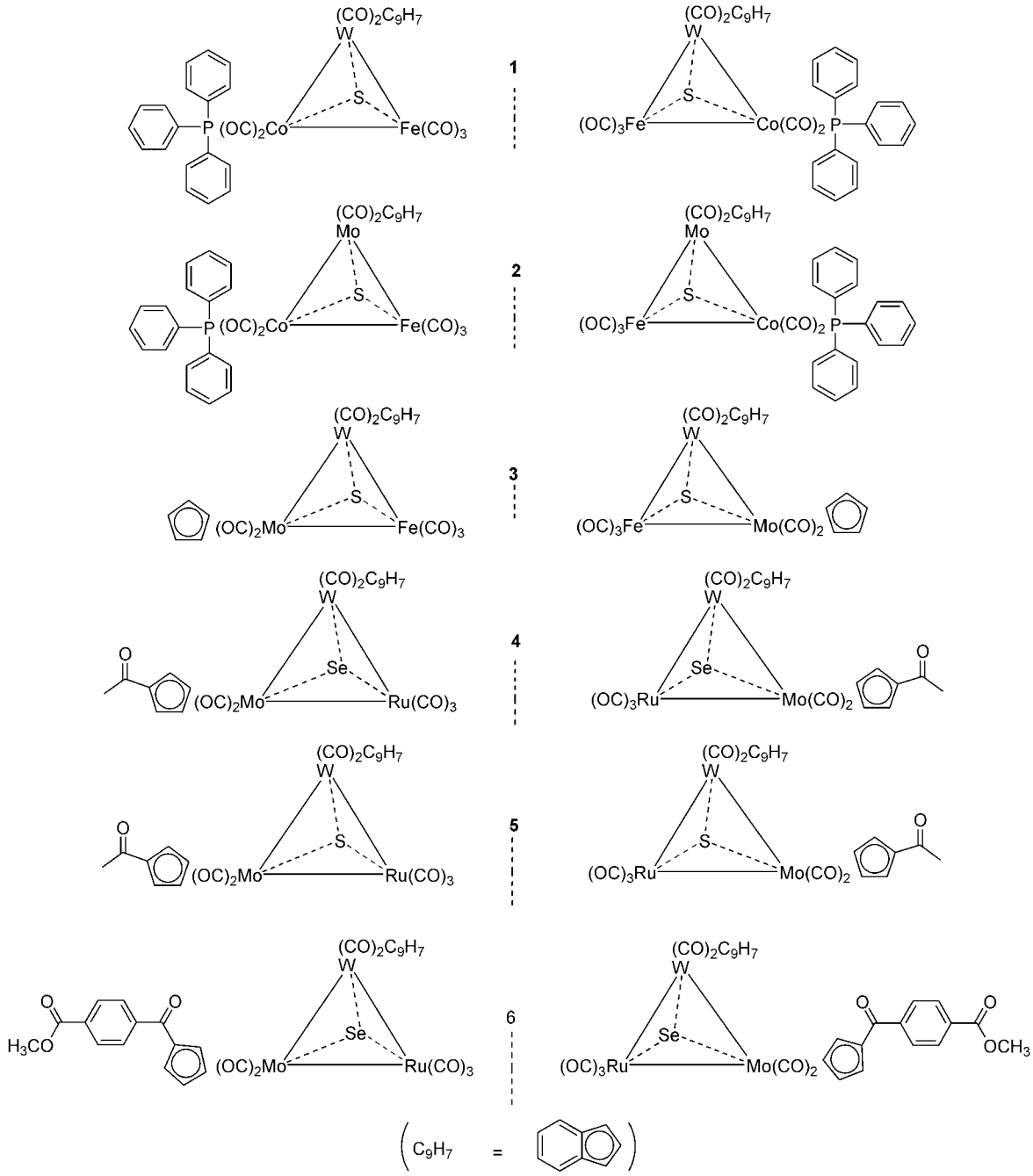

Figure 1 Chemical structures of clusters **1**—**6**.

Comparison of chromatographic behavior of six pair of chiral clusters

The carbamate structural unit has been considered as the most important adsorbing site of the phenylcarbamate derivatives of polysaccharides which are used for chiral recognition.[18] Of the six chiral clusters, **4**—**6** with carbonyl groups can interact with the NH of the carbamate residues through hydrogen bonding interactions; **1** and **2** with proton acceptor (PPh_3) can interact with the CSP in the same way. All of these clusters containing indenyl could interact with the phenyl groups of the ADMPC-CSP by π-π interaction. In addition, the presence of the steric hindrance in the analytes affects their discrimination.

All clusters with indenyl were separated with 1-propanol as mobile phase modifier. Clusters **1** and **2** are of a weaker hydrogen bonding interaction with the CSP, but of a greater steric hindrance, they show a shorter retention and better resolutions than the others. For clusters **4** and **5**, the subtle difference is the element in tetrahedral framework (one is Se, the other S). Cluster **4** can be resolved under all chromatographic conditions. Cluster **5** was not resolved when ethanol was used as a polar modifier. The essential difference between clusters **3** and **5** is that the latter has an acetyl group.

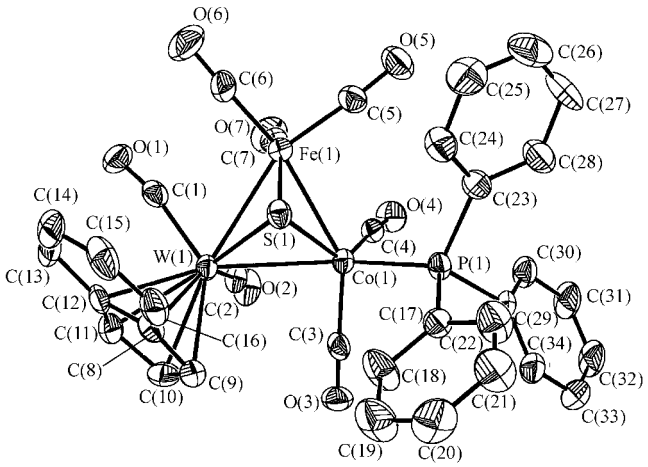

Figure 2 Structure of cluster **1** (ORTEP view).

Cluster **3** was separated by all of these alcohols and gave longer retention than **5**. The best separation was achieved by *n*-hexane/1-butanol used as mobile phase for **3**, then by *n*-hexane/1-butanol for **5**. The difference is something methyl and *para*-methoxycarbonylphenyl between clusters **4** and **6**, and the latter can not be resolved by all these mobile phases apart from 1-propanol used as modifier. It was suggested that the atom in the tetrahedral core and the ligand coordinated to the metal in the tetrahedral core had a significant effect on their chromatographic behavior.

Table 1 Chromatographic parameters of clusters **1**—**6** [a]

Sample	Parameters	95/5	90/10	85/15
	k'_1	3.12	2.38	1.66
1	α	1.46	1.31	1.30
	*R*s	2.45	2.36	2.21
	k'_1	1.72	1.70	1.00
2	α	1.43	1.17	1.16
	*R*s	2.05	1.18	1.13
	k'_1	35.66	20.30	9.39
3	α	1.20	1.18	1.15
	*R*s	1.85	1.16	0.96
	k'_1	16.53	10.07	4.58
4	α	1.18	1.15	1.14
	*R*s	1.17	1.08	1.05
	k'_1	6.41	4.85	2.47
5	α	1.22	1.22	1.20
	*R*s	1.90	1.85	1.43
	k'_1	14.37	7.19	3.80
6	α	1.00	1.00	1.00
	*R*s	0.00	0.00	0.00

[a] (Mobile phase: *n*-hexane/2-propanol, *V*/*V*; flow rate: 1 mL•min^{-1}, λ: 254 nm, 0.02 A.U.F.)

Table 2 Chromatographic parameters of clusters **1**—**6** [a]

Sample	Parameters	Ethanol	1-Propanol	1-Butanol	2-Propanol	*t*-Butanol
	k'_1	2.28	2.14	2.13	2.38	3.54
1	α	1.50	1.30	1.27	1.31	1.15
	*R*s	3.35	1.78	1.77	2.36	0.99
	k'_1	1.79	1.69	1.51	1.70	2.00
2	α	1.35	1.31	1.28	1.17	1.11
	*R*s	2.03	1.99	1.73	1.18	0.82
	k'_1	18.31	17.36	20.78	20.30	34.88
3	α	1.10	1.12	1.20	1.18	1.23
	*R*s	0.88	0.92	2.00	1.16	1.10
	k'_1	9.15	8.16	10.61	10.07	15.04
4	α	1.09	1.17	1.15	1.15	1.12
	*R*s	0.75	1.20	1.18	1.08	0.71
	k'_1	4.62	4.23	4.67	4.85	6.72
5	α	1.00	1.09	1.14	1.22	1.10
	*R*s	0.00	0.72	1.14	1.85	0.72
	k'_1	6.32	6.25	7.02	7.19	14.58
6	α	1.00	1.10	1.00	1.00	1.00
	*R*s	0.00	0.71	0.00	0.00	0.00

[a] (Mobile phase: *n*-hexane/alcohol=90/10, *V*/*V*; flow rate: 1 mL•min^{-1}; λ: 254 nm, 0.02 A.U.F.)

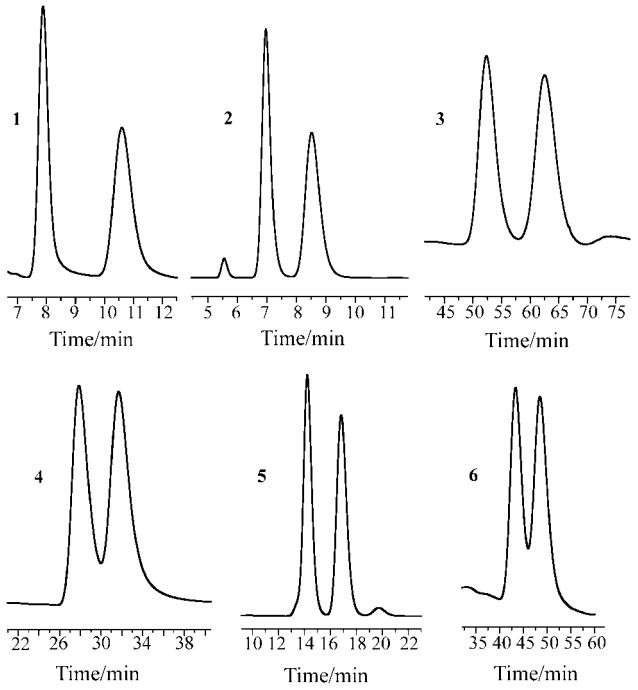

Figure 3 Typical chromatograms of clusters **1**—**6**. Chromatographic conditions: ADMPC-CSP; flow rate, 1.00 mL•min^{-1}; UV detector, 254 nm; Mobile phases; *n*-hexane/ethanol=90/10 (*V*/*V*) for clusters **1** and **2**; *n*-hexane/1-butanol=90/10 for cluster **3**; *n*-hexane/1-butanol=90/10 for cluster **4**; *n*-hexane/2-propanol =90/10 for cluster **5**; *n*-hexane/1-propanol=95/5 for cluster **6**.

Conclusions

ADMPC-CSP is a suitable chiral stationary phase for the optical resolution of chiral tetrahedral metal cluster by HPLC. The results indicated that hydrogen-bonding interaction between the CSP and the chiral cluster seems to play an important role in enantiomeric separation. In general, π-π interactions were stronger and contributed significantly to the retention of chiral clusters on the CSP. In addition, not only the element in the tetrahedral core, but also the metal-chelated ligand would affect the retention and enantioseparation. In future, this method could be used in the enantiomeric preparation of the chiral transition metal tetrahedral clusters.

References

1 Pittman, C. U.; Wilemon, G. M. Jr.; Wilson, W. D.; Ryan, R. C. *Angew. Chem., Int. Ed. Engl*. **1980**, *19*, 478.
2 Vahrenkamp, H. *J. Organomet. Chem*. **1989**, *370*, 65.
3 Yin, Y. Q.; Li, Q. S.; Ding, E. R.; Zhao, Z. Y. *J. Mol. Catal.* **1997**, *11*, 445 (in Chinese).
4 Zhang, W. Q.; Yin, Y. Q.; Han, X. Q.; Chen, L. R. *Sci. China, Ser. B* **2002**, *45*, 481.
5 Zhang, W. Q.; Chen, Z.; Yin, Y. Q. *Chin. Chem. Lett.* **2001**, *12*, 461.
6 Zhang, Y. H.; Yuan, J. C.; Yin, Y. Q.; Zhou, Z. Y.; Chan, Albert, S. C. *New J. Chem*. **2001**, *25*, 939.
7 Zhang, Y. H.; Yuan, J. C.; Yin, Y. Q.; Zhou, Z. Y.; Chan, A. S. C. *Polyhedron* **2001**, *20*, 1859.
8 Ding, E. R.; Yin, Y. Q.; Sun, J. *J. Organomet. Chem*. **1998**, *559*, 157.
9 Zhang, Y. H.; Zhang, W. Q.; Yin, Y. Q. *Chin. Chem. Lett.* **2000**, *12*, 69.
10 Wu, S. L.; Zhou, Z. Q.; Ding, E. R.; Yin, Y. Q. *Chem. J. Chin. Univ.* **1998**, *19*, 1397 (in Chinese).
11 (a) Yashima, E. *J. Chromatogr., A* **2001**, *906*, 105.
(b) Shao, B. H.; Xu, X. Z.; Lü, J. D.; Cai, X. J.; Fu, X. Y. *Acta Chim. Sinica* **2003**, *61*, 440 (in Chinese).
12 Yashima, E.; Okamoto, Y. *Bull. Chem. Soc. Jpn*. **1995**, *68*, 3289.
13 Negawa, M.; Shoji, F. *J. Chromatogr*. **1992**, *590*, 113.
14 Han, X. Q.; Liu, Y. Q.; Zhang, Y. H.; Zhang, W. Q.; Li, Y. M.; Chen, L. R. *Chromatographia* **2002**, *56*, 319.
15 Zhu, X. Y.; Cai, Y. C.; Zhang, W. Q.; Chen, L. R.; Li, Y. M. *J. Chromatogr., A* **2003**, *1002*, 231.
16 Liu, Y. Q.; Han, X. Q.; Qi, B. F.; Liu, C. H.; Li, Y. M.; Chen, L. R. *Chin. J. Chem*. **2002**, *20*, 663.
17 (a) Beurich, H.; Vahrenkamp, H. *Angew. Chem., Int. Ed. Engl*. **1981**, *93*, 128.
(b) Wu, H. P.; Yin, Y. Q.; Yang, Q. C. *Inorg. Chim. Acta* **1996**, *245*, 143.
(c) Bian, Z. G.; Zhang, W. Q.; Guan, H. X.; Yin, Y. Q.; Li, Q. S.; Sun, J. *J. Organomet. Chem*. **2002**, *664*, 201.
18 Okamoto, Y.; Kaida, Y. *J. Chromatogr., A* **1994**, *666*, 403.

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