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Short communication

Enantioseparation of novel chiral heterometal tetrahedral clusters by high-performance liquid chromatography

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Abstract

A series of novel chiral heterometal tetrahedral clusters have firstly been separated on cellulose tris-(3,5-dimethylphenylcarbamate) stationary phase by high-performance liquid chromatography using *n*-hexane as the mobile phase containing different alcohols as modifiers. The effects of concentration and structures of alcohols in the mobile phases and structures of chiral heterometal tetrahedral clusters on enantioseparation were investigated. The results showed that the concentration and structures of alcohols had large effects on enantioseparation. It also was found that both the metal in the tetrahedral core and the ligand coordinated to the atom in tetrahedral core had significant effects on their chromatographic behavior.

Keywords: Chiral stationary phases LC; Enantiomer separation; Mobile phase composition; Cellulose tris-(3,5-dimethylphenylcarbamate); Heterometal tetrahedral clusters

1. Introduction

Chiral heterometal tetrahedral clusters are a kind of organometallic compounds with greatly growing interest because of their potential application as asymmetric reaction catalysts [1–4]. Using a framework chirality cluster as the catalyst, it would not only bring a basic conceptual breakthrough in the asymmetric catalysis, in which the most asymmetric induction originates from the central or planar chirality of P or N ligand, but also extend the methodology in the designs of new chiral catalysts. In recent years, a number of chiral tetrahedral transition metal clusters have been synthesized [5–7], however, enantioseparation of the chiral clusters was still a major problem. The traditional method for enantioseparation was to change the chiral clusters into diastereoisomers firstly and then to separate the diastereoisomers by column chromatography (CC) or thin-layer chromatography (TLC), but the method was time-consuming and inefficient [8], furthermore, it was found that after separation of diastereoisomers the auxiliary optically active group could not be removed without destruction of the cluster [9].

HPLC is one of the efficiency techniques for enantioseparation and requires mild separation conditions. If the tetrahedral cluster enantiomers can be separated directly without derivatization by HPLC on a chiral stationary phase (CSP), the destruction of the cluster will be avoided. There are various types

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of chiral stationary phases available now, among them, cellulose-based CSPs have been proved to be quite versatile. A wide variety of enantiomeric compounds, including chiral aromatic alcohols, enantiomeric amides, pyriproxyfen, amino alcohols, diol, β-blockers, racemic carboxylic acid and other miscellaneous compounds [10] have been separated on these CSPs. Our laboratory has reported some methods for enantioseparation of various chiral compounds [11,12]. It was noted that the cellulose tris-(3,5-dimethylphenylcarbamate) stationary phase was particularly effective.

In this paper, using cellulose tris-(3,5-dimethylphenylcarbamate) chiral stationary phase (CDMPC-CSP), the enantioseparation of six pairs of novel chiral heterometal tetrahedral clusters has firstly been obtained, respectively. Their retention factors (k'), separation factors (α) and the resolutions (R_s) under different mobile phases were compared. The effect of structural variation of the solutes on their enantioseparation was also investigated. Until now, no paper was published on the direct enantioseparation of these novel heterometal tetrahedral clusters on CDMPC-CSP.

2. Experimental

2.1. Instrumentation

The HPLC system consisted of a Waters 515 HPLC pump and a Waters 2487 double absorbance detector (Waters, USA). The chromatographic data were acquired and processed by a Millennium^{32} chromatography manager software (Waters, USA).

2.2. Materials

Microcrystalline cellulose was purchased from The Fourth Reagent Factory of Shanghai (China). 3,5-Dimethylphenylisocyanate was obtained from ACROS (New Jersey, USA). 3-Aminopropyltriethoxy-silane was a product of Liaoning Chemical Plant (China). The spherical silica gel (with a mean particle size of 5 μm, a mean pore diameter of 12 nm and a specific surface area of 110 $m^2\ g^{-1}$) was made in our laboratory. Cellulose tris-(3,5-dimethylphenylcarbamate) was prepared as described in Ref. [13]. CDMPC was coated on aminopropylated silica gel with a coating amount of 15% (w/w). The chiral stationary phase prepared was packed into a stainless steel column (25 cm×4.6 mm) by the conventional high pressure slurry-packing procedure.

Six pairs of heterometal tetrahedral cluster enantiomers were synthesized by the State Key Laboratory for Oxo Synthesis and Selective Oxidation, Lanzhou Institute of Chemical Physics, Chinese Academy of Sciences. All other reagents used were analytical grade from Tianjin Second Chemical Reagent Plant (China).

2.3. Chromatographic conditions

The mobile phase compositions were various alcohols with different percentage in *n*-hexane. The samples were dissolved in mobile phase. All solvents were filtered and degassed in an ultra-sonic bath before use. The flow-rate was 1.5 ml/min. The column temperature was 25 °C. UV detection was performed at 254 nm. The retention factors (k') were determined as $k' = (t_R - t_0)/t_0$. The dead time (t_0) was determined using *n*-hexane as reference. The separation factors (α) were calculated as $\alpha = k'_2/k'_1$, where k'_1 and k'_2 were retention factors for the first and second eluting enantiomer, respectively. The resolutions (R_s) were calculated by the following formula: $R_s = 2(t_2 - t_1)/(w_1 + w_2)$, where w_1 and w_2 are baseline peak widths for the first and second eluting enantiomer, respectively.

3. Results and discussion

The structures of the six pairs of structurally related enantiomers were shown in Fig. 1 and the X-ray structures of clusters B and D were shown in Fig. 2. From the structures of the heterometal tetrahedral cluster enantiomers, it could be found that the chirality of the heterometal tetrahedral clusters is different from the classical chiral organic molecules. There are no distinct monoatomic chiral centers like classical chiral organic molecules; the chirality is due to the general asymmetry of the tetrahedral framework.

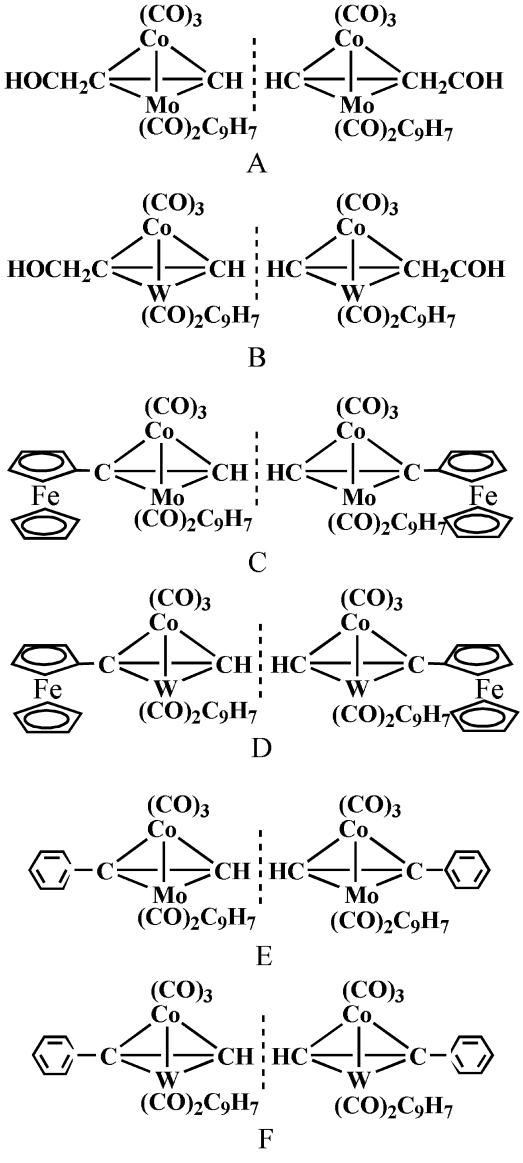

Fig. 1. Structures of the six pairs of chiral heterometal tetrahedral clusters A–F.

In this paper, the effects of various conditions such as the structures and concentration of alcohols in mobile phases and the structural variation of the solutes to be separated were studied. Furthermore, the optimal chromatographic condition for each pair was obtained. Some interesting results were found and discussed.

3.1. Influence of structure of mobile phase modifier (MPM) on retention and enantioselectivity

The effects of the structures of the mobile phase modifiers on retention factors (k'), separation factors (α) and resolutions (R_s) were investigated using a series of alcohols as mobile phase modifiers, the results were presented in Table 1. It could be seen that the retention of clusters changed using different alcohols as MPM. A possible explanation for this change was that there was a competition between the alcohol and the solute to bind with the CSP [14–17]. Different alcohols in mobile phase had different abilities to bind with CSP. If the alcohol could bind with the CSP more strongly, the retention of solute will decrease using it as the mobile phase modifier.

On the other hand, the structure of alcohol had a significant effect on the enantioselectivity. It has been assumed that the alcohol not only competes for binding sites with the solute but also can alter the steric environment of the chiral cavities on the CSP by binding to achiral sites near the chiral cavities. Chiral discrimination between the enantiomers was due to the difference in their steric fit in the chiral cavities of the CSP [14–16]. Alcohols with different structures alter the steric environment of chiral cavities on the CSP differently, thus different enantioselectivity was induced.

3.2. Influence of concentration of MPM on retention and enantioselectivity

From the data shown in Table 2, it was evident that increases in the concentration of alcohol resulted in decreases in the retention factors (k') as expected. For the resolutions (R_s), there were remarkable increases as the concentration of alcohol decreased, whereas too low concentration of alcohol may result in band broadening in some cases.

3.3. Comparison of chromatographic behavior of three types of chiral heterometal tetrahedral clusters on CDMPC-CSP

The six pairs of clusters were classified into three types according to the ligands coordinated to the carbon atom in the tetrahedral core. For clusters A and B, the carbon atom is coordinated by a hydroxy-

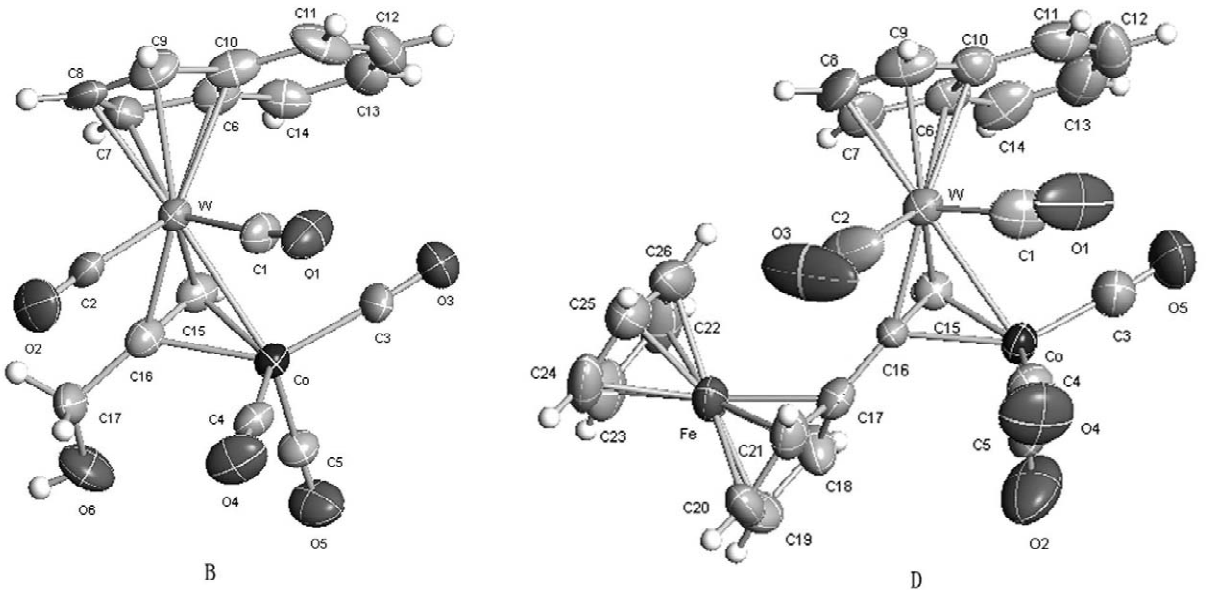

Fig. 2. X-ray structures of clusters B and D.

Table 1
Effect of structure of alcohol modifier on the enantioseparation of clusters A–F

Solute	Parameters	Ethanol	1-Propanol	2-Propanol	1-Butanol	2-Butanol	Tert.-butyl alcohol	2-Pentanol
A	k_1'	2.95	4.57	6.00	4.26	4.98	–	10.38
	α	1.23	1.17	1.11	1.16	1.10	–	1.12
	R_s	1.07	0.82	0.47	0.75	0.36	–	0.53
B	k_1'	3.70	3.14	6.99	6.14	6.83	–	6.38
	α	1.24	1.18	1.11	1.16	1.11	–	1.14
	R_s	1.19	0.76	0.54	0.76	0.44	–	0.61
C	k_1'	1.40	1.51	2.48	–	1.58	2.86	–
	α	1.11	1.11	1.18	–	1.17	1.23	–
	R_s	0.48	0.23	0.71	–	0.58	1.04	–
D	k_1'	2.78	–	4.51	–	2.68	5.27	–
	α	1.12	–	1.12	–	1.13	1.20	–
	R_s	0.39	–	0.78	–	0.40	0.80	–
E	k_1'	0.97	–	–	–	–	–	–
	α	1.16	–	–	–	–	–	–
	R_s	0.63	–	–	–	–	–	–
F	k_1'	1.41	1.81	2.20	–	–	–	1.38
	α	1.41	1.13	1.26	–	–	–	1.22
	R_s	1.42	0.49	1.00	–	–	–	0.61

Mobile phase: *n*-hexane/alcohol = 95/5, v/v, flow-rate: 1.5 ml/min, column temperature: 25 °C, λ = 254 nm.

Table 2
Effect of concentration (%, v/v) of alcohol modifier on the enantioseparation of clusters A–F

Solute	Concentration (%)	k_1'	α	R_s
A	2	7.89	1.22	1.30
	5	2.95	1.23	1.07
	10	1.51	1.22	0.94
B	2	10.61	1.25	1.15
	5	3.70	1.24	1.19
	10	2.30	1.25	1.14
C	2	1.94	1.15	0.59
	5	1.40	1.11	0.48
	10	1.36	1.11	0.29
D	2	3.81	1.12	0.34
	5	2.78	1.12	0.39
	10	1.94	1.12	0.36
E	2	1.63	1.13	0.66
	5	0.97	1.16	0.63
	10	0.84	1.13	0.28
F	2	2.04	1.38	1.55
	5	1.41	1.41	1.42
	10	1.32	1.35	1.41

Mobile phase: *n*-hexane–ethanol, v/v, flow-rate: 1.5 ml/min, column temperature: 25 °C, λ = 254 nm.

methyl ligand; for clusters C and D, the carbon atom is coordinated by a dicyclopentadienyl iron ligand and for clusters E and F, a phenyl group is the ligand (Fig. 1). The enantioseparation conditions were different for three types of chiral clusters. Some general trends regarding the retention and enantioselectivity of the three types of clusters were observed from the data given in Table 1. Clusters A and B could be resolved using ethanol, 1-propanol, 2-propanol, 1-butanol, 2-butanol and 2-pentanol as mobile phase modifiers (MPM) and the optimal MPM was ethanol, but tert.-butyl alcohol was not suitable to be used as the mobile phase modifier for them. Clusters C and D could be resolved by ethanol, 2-propanol, 2-butanol and tert.-butyl alcohol as mobile phase modifiers and the tert.-butyl alcohol were found to be the optimal MPM for them. For clusters E and F, the optimal MPM was ethanol. Some general trends regarding the k' values of the three types of chiral heterometal tetrahedral clusters were observed, Cluster C showed smaller k' values

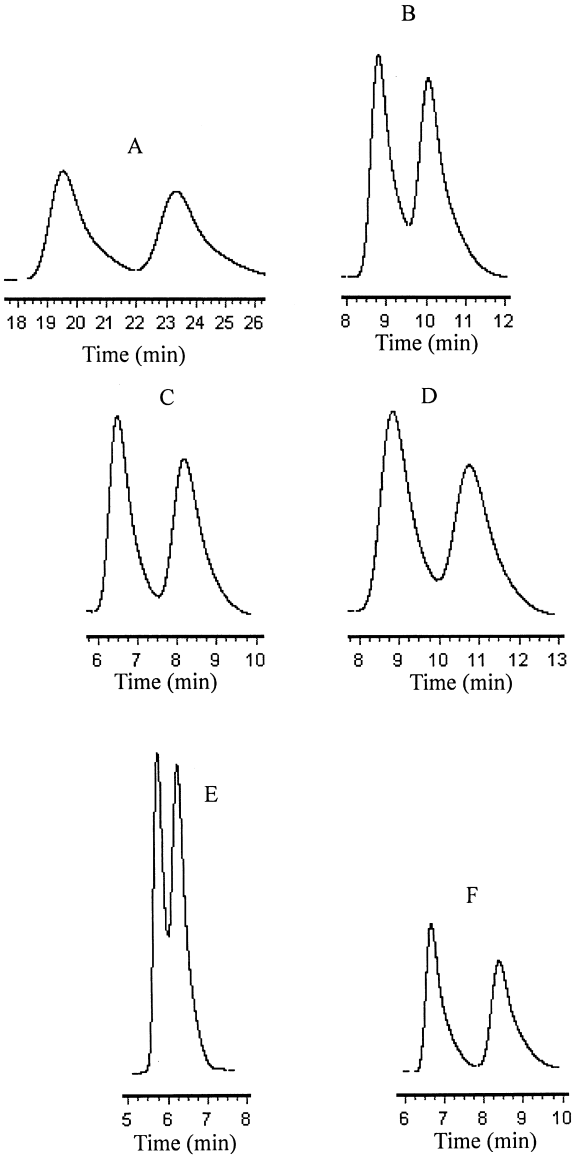

Fig. 3. Optimal chromatograms of clusters A–F. Chromatographic conditions: CDMPC-CSP; flow-rate: 1.5 ml/min; column temperature: 25 °C; UV detector: 254 nm; mobile phase: *n*-hexane-ethanol (98:2, v/v) for A, B, E, F; *n*-hexane-tert.-butyl-alcohol (98:2, v/v) for C and D.

than cluster A under the same mobile phase conditions. However, compared to the k' values of cluster E, the k' values for cluster C were larger. These trends indicated that under identical mobile phase conditions, the degree of retention of the

clusters was in the order of A>C>E. The conditions of clusters with W atoms in their tetrahedral cores also accorded with the trends: B>D>F.

It was suggested that the metal in the tetrahedral core had a large effect on their chromatographic behavior. Clusters with the same ligands had different retention and enantioselectivity under the same mobile phase conditions because of the difference of the metal in the tetrahedral core. For example, although clusters E and F also had similar structures, the differences between their enantioseparation were very large. From the results, it could be seen that cluster F with W atom in the tetrahedral core could be separated using ethanol, 1-propanol, 2-propanol and 2-pentanol as the mobile phase modifiers, but cluster E with Mo atom could be resolved only by ethanol as the mobile phase modifier. Moreover, the k', α, R_s values of cluster E were smaller than cluster F under the same mobile phase conditions.

Under the optimal conditions obtained, six pairs of heterometal tetrahedral cluster enantiomers were well separated, respectively. Fig. 3 shows their typical chromatograms.

4. Conclusion

The enantioseparation of six pairs of chiral heterometal tetrahedral clusters was successfully achieved on CDMPC-CSP by HPLC. The results showed that the structure and the concentration of the alcohol modifier in mobile phase had a large effect on the enantioseparation. The results also showed that both the metal in the tetrahedral core and the ligand coordinated to the atom in the tetrahedral core had significant effects on their enantioseparation.

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