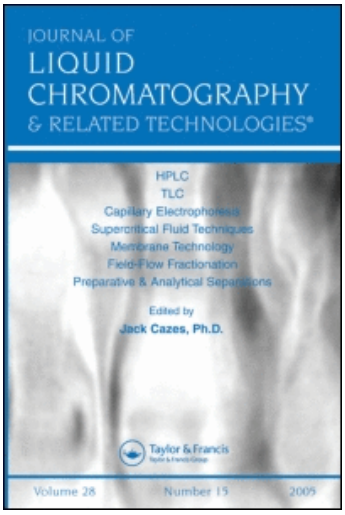

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Separation of Enantiomers of β-Lactams by HPLC Using Cyclodextrin-Based Chiral Stationary Phases

P. Sun[a]; C. Wang[a]; D. W. Armstrong[a]; A. Péter[b]; E. Forró[c]
[a] Department of Chemistry and Biochemistry, The University of Texas at Arlington, Arlington, Texas, USA [b] Department of Inorganic and Analytical Chemistry, University of Szeged, Szeged, Hungary [c] Department of Pharmaceutical Chemistry, University of Szeged, Szeged, Hungary

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Separation of Enantiomers of β-Lactams by HPLC Using Cyclodextrin-Based Chiral Stationary Phases

P. Sun, C. Wang, and D. W. Armstrong
Department of Chemistry and Biochemistry, The University of Texas at Arlington, Arlington, Texas, USA

A. Péter
Department of Inorganic and Analytical Chemistry, University of Szeged, Szeged, Hungary

E. Forró
Department of Pharmaceutical Chemistry, University of Szeged, Szeged, Hungary

Abstract: The enantiomeric separation of 12 β-lactam compounds on 3 native cyclodextrin and 6 derivatized β-cyclodextrin stationary phases was evaluated using high performance liquid chromatography (HPLC). The dimethylphenyl carbamate functionalized chiral stationary phase (CSP) (Cyclobond I 2000 DMP) separated 11 of the 12 β-lactams in the reversed phase mode. The dimethylated β-cyclodextrin column (Cyclobond I 2000 DM) was the second most effective CSP and it separated 8 of the 12 compounds. The reversed phase separation mode was the most effective approach. The effects of the composition and the flow rate on enantioseparations were studied. The effect of the structure of the substituents on the β-lactams was examined.

Keywords: Derivatized cyclodextrin-based stationary phase, Enantiomer, β-Lactam compounds

Address correspondence to Prof. D. W. Armstrong, Department of Chemistry and Biochemistry, The University of Texas at Arlington, Arlington, TX 76019-0065, USA. E-mail: sec4dwa@uta.edu

INTRODUCTION

β-Lactams, including penicillins and cephalosporins, are one of the most widely used types of antibiotics. Their antibacterial function results from the four membered β-lactam ring inhibiting the formation of bacterial cell walls.[1–4] Many synthetic methods have been developed to construct β-lactams with functional groups and defined stereochemistry.[5–8] In addition, β-lactams have been used as important building blocks in the synthesis of other compounds of biological importance, such as amino acids, peptides, and heterocyclic molecules.[9–12]

Stereochemistry greatly affects the synthetic approach, as well as the biological activity of these compounds, so there is a great need for obtaining enantiomerically pure β-lactams. Due to its flexibility, broad selectivity, and high efficiency, liquid chromatography with chiral stationary phases (CSPs) has been widely used for enantioseparations.[13–18] Some enantiomers of β-lactams with aromatic substituents in the 3- or 4-position were separated on an amino acid derived CSP ((S)-N-3,5-dinitrobenzoylleucine).[16] It was reported that a C3, C4 substituted β-lactamic cholesterol absorption inhibitor was separated on an amylose based chiral stationary phases (Chiralpak AD and AS).[17] The enantiomers of 12 β-lactams were separated on two types of CSPs, one of which was a cellulose-tris-3,5-dimethylphenyl carbamate, and the other of which was a macrocyclic glycopeptide antibiotic teicoplanin or teicoplanin aglycone CSP.[18]

Cyclodextrin based CSPs have been widely used to separate chiral compounds,[19–24] especially those with aromatic moities. To our knowledge, this class of chiral stationary phases has not been used for separating bicyclic and tricyclic β-lactams. In this work, the enantioseparation of 12 chiral β-lactams is evaluated by comparing 3 native and 6 derivatized cyclodextrin based CSPs in different chromatographic modes. The effects of the composition of the mobile phase and flow rate on enantioseparation are studied. The effects of the structure of the analytes on retention and selectivity also are discussed.

EXPERIMENTAL

Materials

2-Azetidinone was purchased from Aldrich (Milwaukee, WI, USA). The racemic β-lactams: *cis*-6-azabicyclo[3.2.0]heptan-7-one (1), *cis*-7-azabicyclo[4.2.0]octan-8-one (2), *cis*-7-azabicyclo[4.2.0]oct-3-en-8-one (3), *cis*-7-azabicyclo[4.2.0]oct-4-en-8-one (4), *cis*-8-azabicyclo[5.2.0]nonan-9-one (5), *cis*-9-azabicyclo[6.2.0]decan-10-one (6), *cis*-9-azabicyclo[6.2.0]dec-4-en-10-one (7), *cis*-3,4-benzo-6-azabicyclo[3.2.0]heptan-7-one (8), *cis*-4,5-benzo-7-azabicyclo [4.2.0]octan-8-one (9), *cis*-5,6-benzo-8-azabicyclo[5.2.0]nonan-9-one (10), *exo*-3-

azatricyclo[4.2.1.$0^{2.5}$] nonan-4-one (11) and *exo*-3-azatricyclo[4.2.1.$0^{2.5}$] non-7-en-4-one (12) were prepared by cycloaddition of chlorosulfonyl isocyanate to the corresponding cycloalkenes and cycloalkadienes.[18] They are dissolved in either ethanol or acetonitrile. Ethanol (200 proof) was obtained from Aaper Alcohol and Chemical Company (Shelbyville, KY, USA). Acetonitrile, methanol, tetrahydrofuran (THF), isopropanol, and heptane of HPLC grade were purchased from Fisher Scientific (Fairlawn, NJ, USA). Water was deionized and filtered through active charcoal and a 5 μm filter. Cyclobond I (β-cyclodextrin), II (γ-cyclodextrin), III (α-cyclodextrin), AC (acetylated β-cyclodextrin), DM (dimethylated β-cyclodextrin), RSP (hydroxypropyl ether β-cyclodextrin), DMP (dimethylphenyl carbamate β-cyclodextrin), RN and SN (naphthylethyl carbamate) CSPs were obtained from Advanced Separation Technologies (Whippany, NJ, USA).

Equipment

Chromatographic separations were carried out in three HPLC systems. The first system was a HP (Agilent Technologies, Palo Alto, CA, USA) 1050 system with a UV VWD detector, an autosampler, a quaternary pump, and Chemstation software. The second system consisted of a UV detector (SPD-6A, Shimadzu, Kyoto, Japan), a pump (LC-6A, Shimadzu), a system controller (SCL-10A, Shimadzu), and a chromatographic integrator (SPD-6A, Shimadzu). The third one included a pump (LC-10A, Shimadzu), a UV detector (SPD-10A, Shimadzu), and an integrator (SPD-6A, Shimadzu). In these systems, the samples were injected via a six-port injection valve with a 10 μL sample loop (Rheodyne, Cotati, CA, USA). Mobile phase was degassed by ultrasonication under vacuum for 5 min. All compounds are detected at 210 nm.

Column Evaluation

All CSPs were evaluated in the reversed phase mode using acetonitrile-water, methanol-water, and tetrahydrafuran-water. Except DM, all CSPs were also evaluated in the polar organic mode using acetonitrile/methanol. Aromatic derivatized CSPs (DMP, SN, and RN) were evaluated in the normal phase mode with isopropanol-heptane mobile phase. All separations were carried out at room temperature with the mobile phase flow rate of 1.0 mL/min.

Calculations

The retention factor (k) was calculated using the equation $k = (t_r - t_0)/t_r$, where t_r is the retention time, and t_0 is the dead time, which is determined by the peak of the refractive index change due to the sample solvent.

Selectivity (α) was calculated by $\alpha = k_2/k_1$, where k_1 and k_2 are the retention factors of the first and second eluted enantiomers, respectively. The resolution (R_s) was determined using $R_s = 2 \times (t_{r2} - t_{r1})/(w_1 + w_2)$, where w is the base peak width. The efficiency (the number of theoretical plates, N) was calculated by $N = 16 \times (t_r/w)^2$.

RESULTS AND DISCUSSION

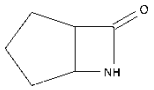
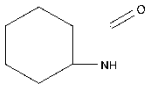
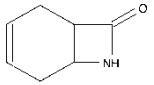
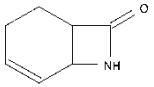
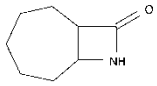
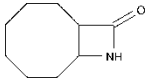
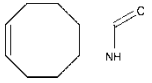
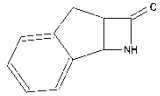
Evaluation

In this work, nine cyclodextrin based CSPs were evaluated for their ability to separate 12 chiral bicyclic or tricyclic β-lactam compounds in the reversed phase mode. Because these β-lactams have no ionizable groups, the pH of the mobile phase does not greatly affect the enantioseparation. Three types of organic modifier were used: methanol, acetonitrile, and tetrahydrofuran. Except for the Cyclobond I 2000 DM CSP, the other eight columns were evaluated in the polar organic mode with acetonitrile/methanol as the mobile phase. In the normal phase mode, the main attractive interactions between analytes and the chiral stationary phase are of the π-π and dipolar types, so only the aromatic derivatized cyclodextrin based CSPs (DMP, RN, and SN) were used in the normal phase mode with heptane/2-propanol as the mobile phase.

In the reversed phase mode, enantioselectivity ($\alpha \geq 1.02$) was observed for all the 12 β-lactams. Table 1 shows the compound structure and the separation results (including k_1', α, R_s, and the mobile phase composition) under optimized conditions. If the chiral analytes are partially separated ($0.3 < R_s < 1.5$), the condition with the largest R_s was selected. When baseline separation occured ($R_s \geq 1.5$), the conditions that produced the smallest k' are given. The results show that seven β-lactams (Compounds **4**, **5**, **6**, **7**, **8**, **9**, and **10**) are baseline separated and five (Compounds **1**, **2**, **3**, **11**, and **12**) are partially separated. Decreasing the flow rate from 1.0 mL/min to 0.5 mL/min improved all the enantioseparations. At the lower flow rate, compounds **4**, **5**, and **7** were baseline separated, while at higher flow rates, they were not.

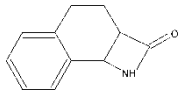
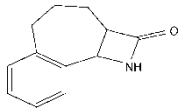
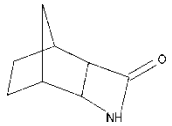
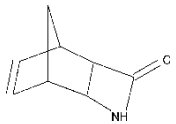
In order to illustrate the effect of the analyte structure on the enantioseparation, Table 1 also includes the chromatographic retention data of compound **13** (2-azetidinone, a nonchiral compound). This compound has greater retention in the polar organic mode (methanol/acetonitrile = 1/99) than in the reversed phase mode (acetonitrile/water = 1/99). It is most strongly retained on the γ-cyclodextrin CSP, with a $k' = 0.91$, shown in Table 1. Enantioresolution varied for different β-lactams and Figure 1 shows selected chromatograms for the best (compounds **9** and **10**), moderate (compounds **5** and **12**), and the worst resolutions (compounds **1** and **3**).

Table 1. Summary of the optimized enantioseparation results

Number	Structure	CSP[a]	k_1	α	R_s[b]	R_s*[c]	Mobile phase (v/v)
1		DMP	3.14	1.06	0.8	0.9	ACN/H_2O = 1/99
2		DMP	7.85	1.07	0.9	0.9	ACN/H_2O = 1/99
3		DMP	3.88	1.08	0.9	1.0	ACN/H_2O = 1/99
4		DMP	4.70	1.11	1.3	1.5	ACN/H_2O = 1/99
5		DMP	3.96	1.10	1.2	1.5	MeOH/H_2O = 30/70
6		DMP	7.40	1.08	1.5	1.6	ACN/H_2O = 15/85
7		DM	2.68	1.14	1.4	1.5	THF/H_2O = 0.1/100
8		DMP	4.20	1.10	1.5	1.9	ACN/H_2O = 15/85

(*continued*)

Table 1. Continued

Number	Structure	CSP[a]	k_1	α	R_s[b]	R_s*[c]	Mobile phase (v/v)
9		DMP	5.20	1.13	1.9	2.4	ACN/H_2O = 15/85
10		DM	2.13	1.20	1.6	2.0	ACN/H_2O = 5/95
11		SN	7.34	1.07	1.2	1.2	ACN/H_2O = 5/95
12		DM	1.24	1.11	1.2	1.3	THF/H_2O = 0.1/99.9
13[d]		II	0.91				MeOH/ACN = 1/99

[a]For the CSP designated by the abbreviations, see Experimental Section.

[b]Obtained at 1.0 mL/min.

[c]Obtained at 0.5 mL/min.

[d]k' on α, β, DMP, DM, RSP, RN, SN, and AC in the reversed phase (acetonitrile/water =1/99) and polar organic mode (acetonitrile/methanol = 99/1) are 0.19 and 0.47, 0.07 and 0.41, 0.23 and 0.57, 0.09, 0.17 and 0.44, 0.22 and 0.42, 0.20 and 0.52, 0.13 and 0.42, respectively.

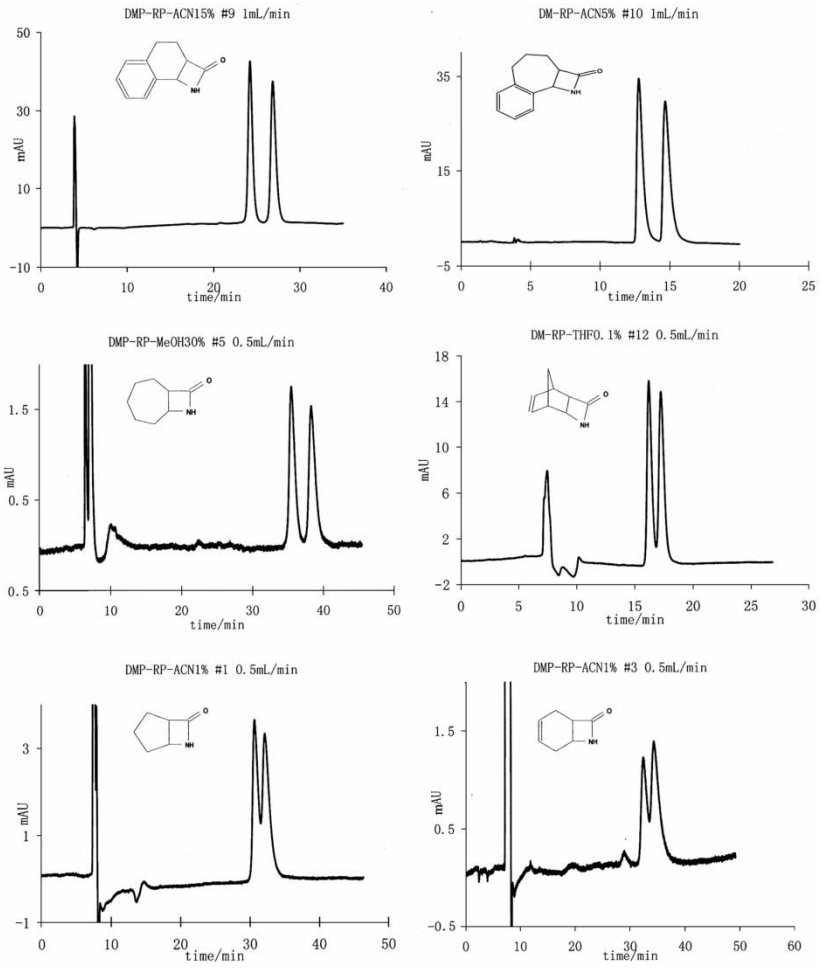


Figure 1. Selected chromatograms showing the best (top two), medium (middle two), and worst (bottom two) enantioseparations for the substituted β-lactams.

Different columns have different selectivities for these β-lactams. Figure 2a shows the performance of nine CSPs. The dimethylphenyl functionalized β-cyclodextrin (Cyclobond I 2000 DMP) is the most effective column for separating these β-lactam enantiomers. It showed enantioselectivity for eleven of the β-lactams (all except compound **12**), including five baseline separations and six partial separations. The dimethylated β-cyclodextrin (Cyclobond I 2000 DM) is the second effective column with two baseline and six partial separations. For the native cyclodextrin CSPs, only γ-cyclodextrin showed any enantioselectivity for these compounds (e.g., for two of the chiral β-lactam compounds). It is apparent that the different functional

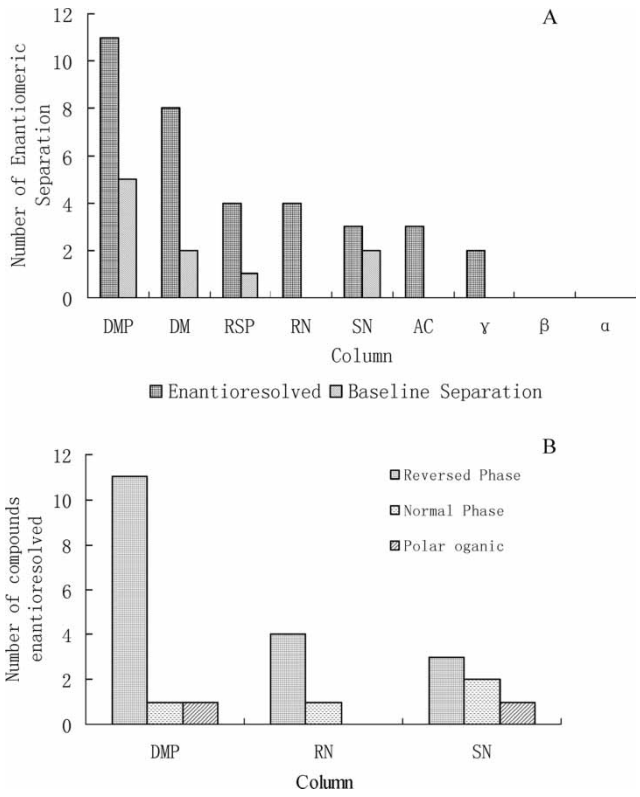


Figure 2. Performance of different cyclodextrin-based CSPs in different separation modes. (A) Overall enantioseparation results for 9 CSPs in all separation modes. (B) Different enantioseparation results in three separation modes on the three aromatic derivatized cyclodextrin CSPs.

groups of the derivatized cyclodextrin CSPs provide enhanced enantioselectivity and expand the usefulness of CSPs based on cyclodextrin.

Only the aromatic derivatized cyclodextrin CSPs (DMP, SN, and RN) can be used to separate enantiomers in all three chromatographic modes (shown in Figure 2b). Eleven compounds are separated in the reversed phase mode on the Cyclobond DMP compared to four on the RN and three on the SN column. In the normal phase mode, the DMP, RN, and SN columns can separate one, one, and two compounds, respectively. In the polar organic mode, only compound **10** was separated on the DMP and SN columns, while the RN column did not achieve any enantioseparations. The separation efficiencies in the reversed phase mode are significantly greater than in the other two modes. Comparing the resolution (R_s) achieved in different modes for the same compound, the reversed phase separations consistently produced larger R_s values for these compounds. The separation of

compound **10** on the Cyclobond I-2000 SN is a good example. With acetonitrile/water (20/80), the R_s is 2.0, while in 100% acetonitrile and 2-propanol/heptane (5/95) the values are 0.5 and 1.0, respectively. The change in enantioresolution in different chromatographic modes depends on the retention mechanism. In the reversed phase mode, inclusion complexation is the dominant retentive interaction, while CSPs form dipolar and π-complexes in the normal phase mode. The hydrogen bonding interactions are the most important in the polar organic mode.

Effect of Mobile Phase on Enantioseparation

Type of Organic Modifier

In the reversed phase mode on Cyclobond CSPs, acetonitrile and methanol are more commonly used than tetrahydrofuran as organic modifiers. The optimized separations for ten of twelve compounds were achieved with acetonitrile or methanol and water as the mobile phase (Table 1). The best separations for compounds **7** and **12** were achieved with tetrahydrofuran (THF)-water mobile phases. Comparing acetonitrile and methanol as organic modifiers, acetonitrile is more successful mainly due to the higher chromatographic efficiencies produced; the selectivity was similar for most compounds. In some specific cases, changing from acetonitrile to methanol has a notable effect on enantioselectivity. For example, using acetonitrile/water as the mobile phase, no selectivity for compound **10** was seen on the Cyclobond I 2000 DMP column, while it was partially separated with a methanol-water mobile phase, as shown in Figure 3.

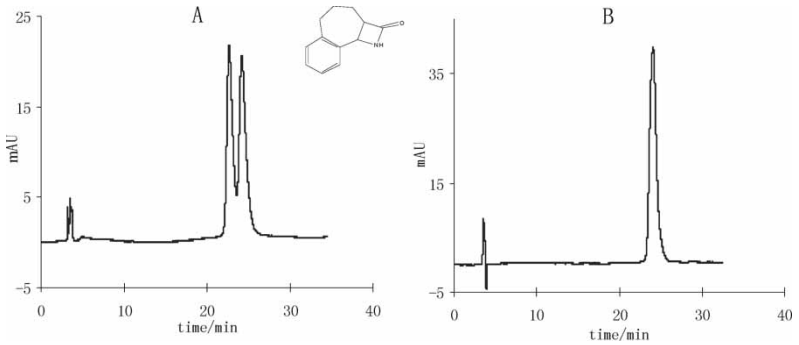


Figure 3. Comparison of separations resulting from the use of different organic modifiers. Compound 10 was separated on the Cyclobond I 2000 DMP column using the following mobile phases: A) 70/30 water/methanol and B) 85/15 water/acetonitrile.

Concentration of Organic Modifier

When operating in the reversed phase mode, an important interaction between the CSPs and analytes is the hydrophobic inclusion complex. Organic solvents compete with the analytes for the nonpolar cavity of the cyclodextrin, so the analytes are more strongly retained when the concentration of the organic modifier is decreased. Changing the concentration of organic modifier changes the retention, selectivity, and resolution. Table 2 lists the separation results for compound **10** as separated on the Cyclobond I 2000 SN column. When the percentage of acetonitrile is below 80%, decreasing the concentration of acetonitrile increases the retention, enantioselectivity, and resolution of the analytes. However, when the percentage of acetonitrile is above 80%, the reverse trend is obtained. In pure acetonitrile (the polar organic mode), a partial separation ($R_s = 0.6$, $\alpha = 1.08$) was obtained.

Flow Rate of the Mobile Phase

Changing the flow rate of the mobile phase affects the efficiency of liquid chromatography. The effect of flow rate for the separation was investigated for compound **12** on the Cyclobond I 2000 SN column with a THF/water (1/99) mobile phase (shown in Table 3). When decreasing the flow rate from 1.0 mL/min to 0.2 mL/min, the selectivity (in the range of 1.128–1.130) and the retention factor (0.64) are the same within experimental

Table 2. Effect of concentration of organic modifier on the separation parameters for compound **10**[a]

Percent of acetonitrile	k_1	α	R_s
0	20.78	1.39	3.4
5	7.40	1.27	2.2
10	5.04	1.25	2.1
15	3.33	1.19	1.8
20	2.23	1.15	1.4
30	0.92	1.10	1.1
40	0.73	1.05	0.6
50	0.59	1.00	0
60	0.46	1.00	0
70	0.23	1.00	0
80	0.18	1.00	0
90	0.25	1.00	0
100	0.63	1.08	0.6

[a]The results for compound **10** were obtained on the Cyclobond I 2000 SN column.

Table 3. Effect of the flow rate of the mobile phase[a]

Fow rate (mL/min)	k_1	α	R_s	N
1.0	0.64	1.13	0.99	7040
0.9	0.64	1.13	1.06	7530
0.8	0.64	1.13	1.09	7620
0.7	0.64	1.13	1.10	7940
0.6	0.64	1.13	1.12	8080
0.5	0.64	1.13	1.13	8110
0.4	0.64	1.13	1.13	8160
0.3	0.64	1.13	1.13	8140
0.2	0.64	1.13	1.14	8170

[a]The results for compound **12** were obtained on the SN column using tetrahydrofuran/water (1/99) as mobile phase.

error. The main factor contributing to the change of resolution is efficiency (N_1, the number of theoretical plates of the first peak). Decreasing the flow rate from 1.0 to 0.2 mL/min improved the efficiency (N increased from 7040 to 8200) and resolution slightly (R_s changed from 0.99 to 1.14). In some cases, the flow rate shows a larger effect on chromatographic separation. In Table 1, decreasing the flow rate from 1.0 mL/min to 0.5 mL/min improves the resolution of compound **9** from 1.9 to 2.4.

Effect of Analyte Structure

It was found that the simple, unsubstituted lactam (compound **13**) has very little retention on any column and under any of the mobile phase conditions (Table 1). Clearly, the hydrophobicity provided by the cyclic or bicyclic hydrocarbon substituent is essential for retention in the reversed phase mode, and this substituent structure affects enantioselectivity as well.

In the reversed phase mode, solute retention results from an inclusion complex formation with the cyclodextrin cavity, and this is affected by the hydrophobicity of the solutes. Figure 4 indicates that the size of the substituent ring of the β-lactams affects the retention greatly. An examination of the retention results of compounds **1**, **2**, **5**, and **6** on the Cyclobond DM column reveals that the size increase from a five membered to eight membered ring enhances the retention due to higher hydrophobicity.

The presence of an aromatic ring is beneficial to chiral recognition on Cyclobond based CSP as well. Comparison of compounds **1** and **8**, **2**, and **9** on the Cyclobond I 2000 DMP column (shown in Table 1) shows the effect of addition of an aromatic ring. The Cyclobond DMP CSP shows baseline resolution for compounds **8** ($R_s^* = 1.9$) and **9** ($R_s^* = 2.4$), but not for **1** ($R_s^* = 0.9$) and **2** ($R_s^* = 0.9$) under optimized conditions.

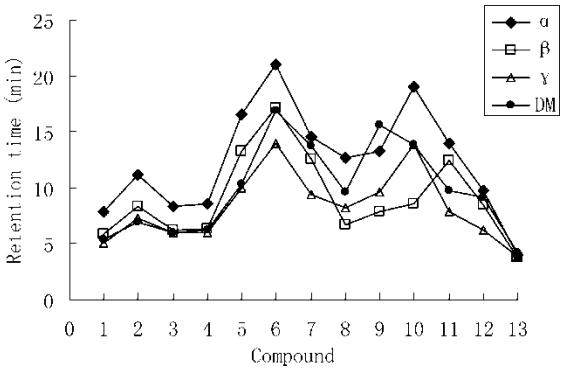


Figure 4. Retention times of 13 β-lactams on four cyclodextrin-based CSPs (α, β, γ, and DM). Note: the mobile phase for α, β, γ,-cyclodextrin CSPs is acetonitrile-water (1/99), while it is acetonitrile-water (5/95) for Cyclobond I-2000 DM CSP.

The presence of a double bond also has a beneficial effect on enantioseparation. Comparison of the chromatographic results of compounds **2**, **3**, and **4** on the Cyclobond DM column is a good example. Compared to **2**, compounds **3** and **4** have a double bond, which are positioned differently in the ring. It was observed that adding a double bond decreased the retention (shown in Figure 4) while enhancing selectivity. Cyclobond DM CSP shows enantioselectivity for compound **4**, but not for compounds **2** and **3**.

CONCLUSIONS

Enantioseparation of 12 β-lactams was achieved on nine cyclodextrin based CSPs. Baseline separation was observed for seven compounds. The Cyclobond DMP column was the most effective stationary phase in that it separated 11 of 12 substituted β-lactams. The cyclobond DM also was effective and separated 8 of 12 β-lactams. The cyclobond RSP, RN, SN, AC, and γ cyclodextrin CSPs showed enantioselectivity for a few β-lactams, while the native α and β-cyclodextrin CSPs did not show any enantioselectivity for these analytes. The reversed phase mode was the most effective approach and only two separations were observed in the normal phase and polar organic modes. The composition of organic modifier and the flow rate affect all enantioseparations. The substituents on the β-lactams contribute much to retention and enantioselectivity. In particular, more rigid aromatic and tricyclic compounds produced the greatest separation factors and resolutions.

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