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Separation of chiral furan derivatives by liquid chromatography using cyclodextrin-based chiral stationary phases

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Abstract

The enantiomeric separation of a set of 30 new chiral furan derivatives has been achieved on native and derivatized β-cyclodextrin stationary phases using high performance liquid chromatography (HPLC). The hydroxypropyl-β-cyclodextrin (Cyclobond RSP), the 2,3-dimethyl-β-cyclodextrin (Cyclobond DM), and the acetyl-β-cyclodextrin (Cyclobond AC) stationary phases are the most effective chiral stationary phases (CSPs) for the separation of these racemates in the reverse phase mode. No enantioseparations have been observed on the native β-cyclodextrin chiral stationary phase (Cyclobond I 2000) and only a few separations have been attained on the *S*-naphthylethyl carbamate β-cyclodextrin (Cyclobond SN) and 3,5-dimethylphenyl carbamate β-cyclodextrin (Cyclobond DMP) chiral stationary phases in the reverse phase mode. The polar organic and the normal phase mode on these CSPs are not effective for separation of these compounds. The characteristics of the analytes, including steric bulk, hydrogen bonding ability, and geometry, play an important role in the chiral recognition process. The pH affects the enantioseparation of compounds with ionizable groups and the addition of 0.5% methyl *tert*-butyl ether to the mobile phase significantly enhances the separation efficiency for some highly retained compounds.

Keywords: Chiral separation; Enantioseparation; Chiral stationary phase; Cyclodextrin; Derivatized cyclodextrins; Chiral furan derivatives

1. Introduction

Furan derivatives are important structure units in a variety of natural products and pharmaceuticals [1–3]. Furanosesquiterpenes [4] are metabolites found in many marine invertebrates. Richardianidins [5] are isolated from the leaves of the plant *Cluytia richardiana* and the melatonin receptor agonist drug candidate TAK-375 [6] has a chiral substituted furan structure. Furthermore, chiral furan derivatives are important building blocks in synthetic organic chemistry [7–11]. Oxidative cleavage of the furan ring under mild conditions allows certain furans to be converted to amino acids [12–14]. Piperidines and aza sugars can be obtained by the aza-*Achmatowicz* reaction from furan derivatives [15–17]. Furans also can act as dienes, and participate in [4 + 2] cycloaddition reactions with alkenes, alkynes or allenes, to form many important compounds [18–21].

Recently, Yao and Larock have synthesized a series of new chiral furans through the cyclization-cross-coupling of 2-(1-alkynyl)-2-alken-1-ones with various nucleophiles using auric chloride catalysis (Fig. 1) [22]. Alternatively, one can employ I_2, rather than $AuCl_3$, to form iodofurans [23]. The stereogenic center adjacent to the furan ring is generated by the attack of nucleophile on the alkene portion of the starting material. The potential of these compounds as drug candidates and/or useful synthetic intermediates is promising. It is well known that different enantiomers of a chiral compound show different biological activities [24]. Therefore, separation and assessment of the properties of these new chiral furans are necessary.

Cyclodextrin-based chiral stationary phases (Fig. 2), due to their ability to separate enantiomers of many chiral compounds [25–28] and especially neutral chiral

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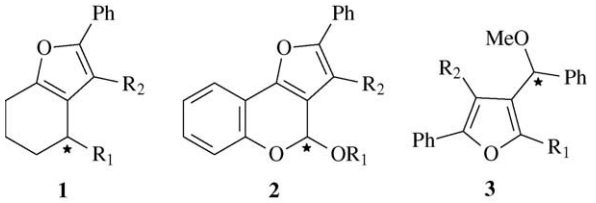


Fig. 1. Structure **1** is a tetrahydrobenzofuran derivative. Structure **2** is a furochromene derivative. Structure **3** is a simple multiply-substituted furan. R_1 can be various types of aliphatic or aromatic substituents. R_2 can be an iodine or a hydrogen atom. The carbon marked with an asterisk is the stereogenic center.

molecules with aromatic units [29–34], are a natural choice for the separation of these new chiral furan derivatives. One previous publication has described the separation of two chiral substituted furans (racemic 1-(2-furylethyl) prenyl ether and racemic *anti*-3-isopropenyl-12-methyl-13-oxabicyclo[8.2.1]trideca-1(12), 10-dien-2-ol) using GC with a heptakis(2,3,6-tri-*O*-methyl)-β-cyclodextrin column, and also by SFC and LC with a carbamoylated cellulose and amylose chiral stationary phases [35]. To our knowledge, no other systematic or individual enantioseparations of chiral furans have been reported. In this work, the enantioselectivity of native and derivatized cyclodextrin based chiral stationary phases for 30 new chiral substituted furans was evaluated in different chromatographic modes. The cyclodextrin-based CSPs show enantioselectivity for 28 compounds and baseline separated 16 of them. The effects of analyte structure and the composition of the mobile phase on the enantioseparations are discussed.

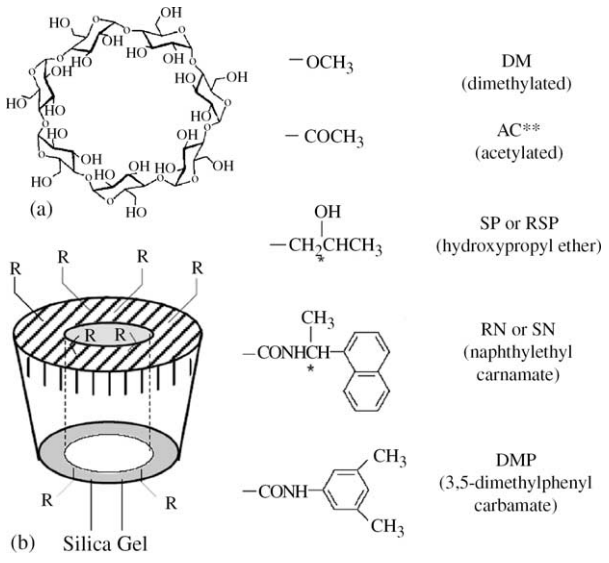


Fig. 2. (a) Native β-cyclodextrin (Cyclobond I 2000). (b) Types of derivatized β-cyclodextrins. An asterisk denotes the chiral center. Taken from Cyclobond Handbook, 6th edition, 2002 with permission.

2. Experimental

2.1. Materials

Cyclobond I 2000, DM, AC, RSP, DMP, and SN CSPs were obtained from Advanced Separation Technologies (Whippany, NJ, USA). All stationary phases used consisted of the chiral selector bonded to 5 μm spherical silica gel [27,28]. The chiral selectors used are the native β-cyclodextrin and its derivatives, which are shown in Fig. 2. The dimensions of the columns are 250 mm × 4.6 mm. Methanol, acetonitrile, 2-propanol, heptane, and methyl *tert*-butyl ether were HPLC grade from Fisher (Fairlawn, NJ, USA). Triethylamine, and acetic acid were ACS certified grade from Fisher. Water was deionized and filtered through active charcoal and a 5 μm filter.

2.2. Preparation of chiral furan derivatives

All chiral furan derivatives were prepared as previously reported via cyclization of 2-(1-alkynyl)-2-alken-1-ones with various nucleophiles using auric chloride catalysis [22] or iodine [23]. The general procedure is as below:

A solution of $AuCl_3$ (30.3 mg) in acetonotrile (970 mg) was prepared. To the appropriate 2-(1-alkynyl)-2-alken-1-one (0.2 mmol) and nucleophile (1.5 equiv.) in dichloromethane (1 ml), was added the above $AuCl_3$ solution (20 mg, 1 mol%). The mixture was stirred at room temperature for 1 h unless otherwise specified. The solvent was removed under vacuum and the residue was purified by flash chromatography on silica gel.

2.3. Equipment

Chromatographic separations were carried out using a HP 1050 HPLC system with a UV VWD detector, an auto sampler, and computer controlled Chem-station data processing software. The mobile phases were degassed by ultra-sonication under vacuum for 10 min. UV detection was carried out at 300 nm for most of the compounds, except compound **18**, which was detected at 254 nm. All separations were carried out at room temperature (∼23 °C).

2.4. Column evaluation

The performance of each stationary phase was evaluated in the reverse phase mode using acetonitrile–water and methanol–water mobile phases. Cyclobond I 2000, AC, RSP, SN, and DMP CSPs were evaluated in the polar organic mode using acetonitrile and the Cyclobond SN and DMP CSPs were evaluated in the normal phase mode using isopropanol–heptane. The flow rate of the mobile phase optimized for resolving the enantiomers of each compound was 1.0 ml/min.

2.5. Calculations

The dead time (t_0) was estimated using the peak resulting from the change in refractive index from the injection solvent on each CSP. The retention factor (k) was calculated using the equation $k = (t_r - t_0)/t_0$. The enantioselectivity (α) was calculated using $\alpha = k_2/k_1$. The resolution factor (R_S) was calculated using the equation $R_S = 2 \times (t_{r2} - t_{r1})/(w_1 + w_2)$, where t_{r2} and t_{r1} are the retention times of the second and first enantiomers, respectively, and w_1 and w_2 are the corresponding base peak widths. The efficiency (number of theoretical plates, N) was calculated using $N = 16(t_r/w)^2$.

3. Results and discussion

3.1. Performance of the CSPs

All of the 30 substituted chiral furans, including 22 tetrahydrobenzofuran derivatives, four furochromene derivatives, and four simple, multiply-substituted furans have been assessed on six different cyclodextrin-based CSPs in the reverse phase mode. The polar organic mode and normal phase mode have been utilized with five CSPs (except the Cyclobond DM CSP) and two aromatically derivatized cyclodextrin CSPs, respectively. The chromatographic data for all successful and several unsuccessful separations are given in Tables 1 and 2. Most compounds were eluted at the dead volume of the column in the polar organic mode under the weakest solvent condition (100% acetonitrile) for this separation mode and no enantioseparation was observed for the compounds that were retained. All analytes were retained in the normal phase mode with a 1:99 isopropanol–heptane mobile phase, but only one partial diastereomeric separation was observed for compound **5** on the Cyclobond SN CSP. For reverse phase LC, enantioseparations ($\alpha > 1.02$) were observed for 28 compounds and 16 baseline separations ($R_S > 1.5$) were achieved. The performance of each CSP in the reverse phase mode is summarized in Fig. 3 and Table 1. Obviously, the most effective CSPs for resolving these chiral substituted furans are Cyclobond DM, RSP, and AC CSPs. The Cyclobond DM CSP was able to separate 19 of the enantiomers with 10 baseline separations. Eighteen enantioselective and five baseline separations were observed on the Cyclobond RSP column. The Cyclobond AC column also showed enantioseparations of 11 analytes and baseline separation of five of them. The remaining CSPs, Cyclobond I 2000 and the aromatic derivatized Cyclobond SN and DMP CSPs were either ineffective or showed enantioseparation for only a few of the examined chiral furans in the reverse phase mode. The separation data for these CSPs are summarized in Table 2.

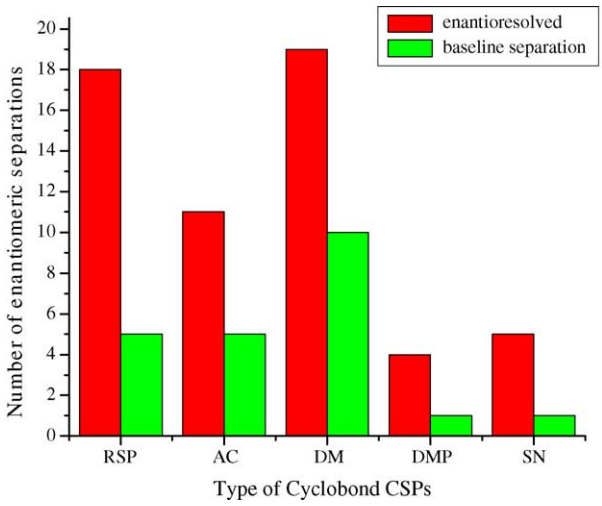


Fig. 3. Summary of the number of baseline and partial separations obtained on different CSPs.

3.2. Effect of mobile phase composition

For separations in the reverse phase mode, two organic modifiers, acetonitrile and methanol, were examined. In general, similar enantioseparations were observed with both organic modifiers. Compared to methanol, acetonitrile has greater solvent strength in the reverse phase mode and a higher affinity for the cyclodextrin cavity; therefore, less retention and enantioselectivity were found when using acetonitrile as opposed to methanol at equivalent volume-based mobile phase compositions.

The effect of the pH of the buffer was also assessed. All 30 compounds were investigated on all of the examined CSPs with 0.1% TEAA (triethylamine/acetic acid) buffer solution from pH 4 to 8. No appreciable difference in selectivity or resolution was observed for the neutral compounds. However, a mobile phase pH effect on the enantioseparation of compounds **3**, **7** and **14**, which contain ionizable groups, was observed. Table 3 shows the separation data for these three compounds at different pH values. For example, compound **7**, which has a weakly basic indole group, shows an appreciable decrease in retention at pH 4 on the Cyclobond DM CSP. At other pHs, the retention, selectivity, and resolution were similar. For compound **14** with a dimethyl aniline group, the reduction in retention at pH 4 was observed with both the Cyclobond RSP and AC CSPs. The separation data at all other pHs from 5 to 8 are quite similar. Compared to the separation achieved in a water/methanol mobile phase, the retention decreased, while the resolution increased, at all pHs. Since the enantioselectivity (α-value) is similar, the increase in resolution is due to the increase in efficiency. The greatest effect of pH on retention, selectivity, and resolution was found for compound **3**, which has a carboxylic acid group (Fig. 4). Although good enantioselectivity was achieved with a methanol/water mobile phase, the efficiency was so poor that the resolution was only 0.8. When using methanol/buffer as the mobile phase, the retention decreased and sharper peaks with better resolution were achieved. The best separation was attained at pH 5 (Fig. 4). With an increase in the pH of the buffer, the analyte is ionized and

Table 1
Retention factor of the first peak (k_1), enantioselectivity (α), and enantioresolution (R_S) of all chiral furans on the Cyclobond RSP, DM, and AC CSPs

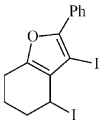
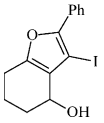
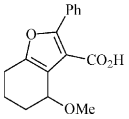
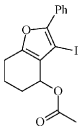
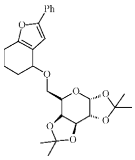
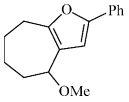
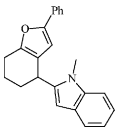
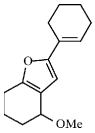
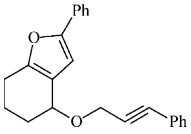
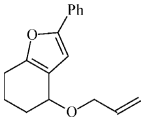
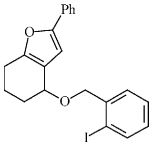
Number	Structure	CSP	k_1	α	R_S	Mobile phase (v/v)
1		RSP	8.52	1.05	0.3	CH_3OH/H_2O = 50/50
		DM	7.59			CH_3OH/H_2O = 50/50
		AC	8.38			CH_3OH/H_2O = 50/50
2		RSP	8.58	1.10	1.2	CH_3OH/H_2O = 45/55
		DM	7.46	1.23	1.9	CH_3OH/H_2O = 25/75
		AC	4.57			CH_3OH/H_2O = 40/60
3		RSP	3.48			CH_3OH/H_2O = 40/60
		DM	2.03			CH_3OH/H_2O = 40/60
		AC	8.15	1.30	0.8	CH_3OH/H_2O = 60/40
4		RSP	10.38	1.05	0.5	CH_3OH/H_2O = 45/55
		DM	5.13	1.13	1.2	CH_3OH/H_2O = 40/60
		AC	5.04	1.13	0.8	CH_3OH/H_2O = 40/60
5[a]		RSP	8.89			CH_3OH/H_2O = 50/50
		DM	2.12			CH_3OH/H_2O = 40/60
		AC	2.55			CH_3OH/H_2O = 50/50
6		RSP	3.35			CH_3OH/H_2O = 60/40
		DM	2.72	1.48	2.6	CH_3OH/H_2O = 40/60
		AC	2.79			CH_3OH/H_2O = 50/50
7		RSP	5.43	1.17	1.7	CH_3OH/H_2O = 60/40
		DM	3.94	1.35	1.6	CH_3OH/H_2O = 50/50
		AC	5.52			CH_3OH/H_2O = 50/50
8		RSP	7.14			CH_3OH/H_2O = 60/40
		DM	4.08	1.29	1.9	CH_3OH/H_2O = 40/60
		AC	3.69			CH_3OH/H_2O = 50/50
9		RSP	4.31	1.06	0.6	CH_3OH/H_2O = 60/40
		DM	8.75	1.10	0.4	CH_3OH/H_2O = 40/60
		AC	9.33			CH_3OH/H_2O = 50/50
10		RSP	2.24			CH_3OH/H_2O = 60/40
		DM	2.52	1.32	2.0	CH_3OH/H_2O = 40/60
		AC	2.57			CH_3OH/H_2O = 50/50
11		RSP	12.79			CH_3OH/H_2O = 50/50
		DM	6.96	1.26	1.0	CH_3OH/H_2O = 40/60
		AC	5.98			CH_3OH/H_2O = 50/50

Table 1 (*Continued*)

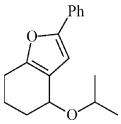
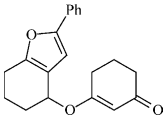
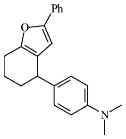
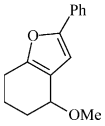
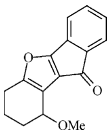
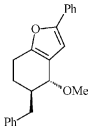
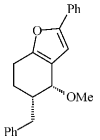
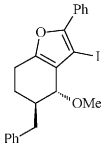
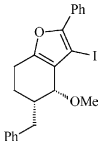
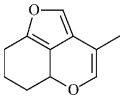
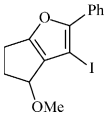
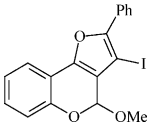
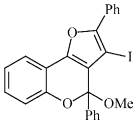
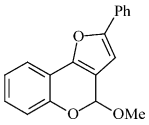
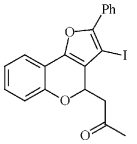
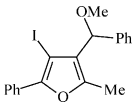
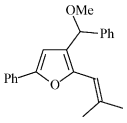
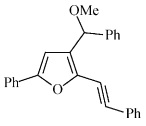
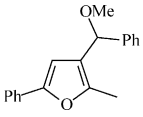
Number	Structure	CSP	k_1	α	R_S	Mobile phase (v/v)
12		RSP	4.76	1.03	0.3	CH_3OH/H_2O = 50/50
		DM	1.57	1.34	1.7	CH_3OH/H_2O = 40/60
		AC	4.95	1.08	0.8	CH_3OH/H_2O = 40/60
13		RSP	2.77			CH_3OH/H_2O = 60/40
		DM	4.06			CH_3OH/H_2O = 40/60
		AC	7.81	1.13	1.4	CH_3OH/H_2O = 40/60
14		RSP	8.97	1.37	2.9	CH_3OH/H_2O = 60/40
		DM	6.28			CH_3OH/H_2O = 50/50
		AC	6.94	1.36	2.4	CH_3OH/H_2O = 50/50
15		RSP	4.40	1.03	0.3	CH_3OH/H_2O = 50/50
		DM	9.57	1.28	1.7	CH_3OH/H_2O = 40/60
		AC	5.76			CH_3OH/H_2O = 40/60
16		RSP	7.64	1.13	1.2	CH_3OH/H_2O = 40/60
		DM	1.66			CH_3OH/H_2O = 40/60
		AC	3.32			CH_3OH/H_2O = 40/60
17		RSP	8.69	1.11	1.2	CH_3OH/H_2O = 60/40
		DM	12.60	1.10	0.6	CH_3OH/H_2O = 40/60
		AC	11.40	1.17	1.6	CH_3OH/H_2O = 40/60
18		RSP	7.00			CH_3OH/H_2O = 60/40
		DM	6.95	1.55	3.1	CH_3OH/H_2O = 40/60
		AC	10.83	1.09	0.9	CH_3OH/H_2O = 40/60
19		RSP	6.02	1.15	1.5	CH_3OH/H_2O = 60/40
		DM	4.50	1.27	1.2	CH_3OH/H_2O = 50/50
		AC	9.88	1.31	1.6	CH_3OH/H_2O = 40/60
20		RSP	4.00			CH_3OH/H_2O = 60/40
		DM	7.37	1.22	1.0	CH_3OH/H_2O = 40/60
		AC	7.75			CH_3OH/H_2O = 40/60
21		RSP	3.13	1.17	1.5	CH_3OH/H_2O = 60/40
		DM	4.64	1.34	2.8	CH_3OH/H_2O = 40/60
		AC	5.33	1.23	2.2	CH_3OH/H_2O = 40/60
22		RSP	10.99	1.09	1.1	CH_3OH/H_2O = 45/55
		DM	4.09	1.28	1.7	CH_3OH/H_2O = 40/60
		AC	6.59			CH_3OH/H_2O = 40/60
23		RSP	14.24	1.12	1.5	CH_3OH/H_2O = 45/55
		DM	9.57			CH_3OH/H_2O = 35/65
		AC	6.28			CH_3OH/H_2O = 40/60

Table 1 (*Continued*)

Number	Structure	CSP	k_1	α	R_S	Mobile phase (v/v)
24		RSP	7.52			CH_3OH/H_2O = 50/50
		DM	8.26	1.11	0.6	CH_3OH/H_2O = 40/60
		AC	5.25			CH_3OH/H_2O = 50/50
25		RSP	5.43	1.06	0.6	CH_3OH/H_2O = 50/50
		DM	6.99	1.15	1.2	CH_3OH/H_2O = 35/65
		AC	5.59	1.04	0.3	CH_3OH/H_2O = 40/60
26		RSP	9.05	1.11	1.1	CH_3OH/H_2O = 45/55
		DM	3.71			CH_3OH/H_2O = 40/60
		AC	3.04			CH_3OH/H_2O = 50/50
27		RSP	7.34			CH_3OH/H_2O = 50/50
		DM	4.83			CH_3OH/H_2O = 40/60
		AC	5.84			CH_3OH/H_2O = 40/60
28		RSP	3.43			CH_3OH/H_2O = 50/50
		DM	2.28			CH_3OH/H_2O = 50/50
		AC	2.88			CH_3OH/H_2O = 50/50
29		RSP	4.24	1.08	0.7	CH_3OH/H_2O = 60/40
		DM	3.86			CH_3OH/H_2O = 50/50
		AC	8.97			CH_3OH/H_2O = 50/50
30		RSP	4.95	1.05	0.6	CH_3OH/H_2O = 50/50
		DM	5.78	1.10	0.8	CH_3OH/H_2O = 40/60
		AC	5.71	1.11	0.7	CH_3OH/H_2O = 40/60

[a] Separation of diastereomers.

more hydrophilic. Thus, both the retention and resolution decrease.

It has been reported that the addition of a small amount of methyl *tert*-butyl ether in the mobile phase can improve the peak shape and efficiency for some analytes with high enantioselectivity, but very poor efficiency, due to stationary phase mass transfer effects (often due to very strong inclusion in the cyclodextrin cavity) [31]. In this work, there appear to be two such cases. They involve the separations of compounds **14** and **15** on the Cyclobond DM and Cyclobond AC CSPs, respectively. These separations afforded broad, asymmetric peak shapes, but they retained significant peak-to-peak separations (Fig. 5a and c). An appreciable decrease in retention and great increase in efficiency were observed for both compounds with the addition of a small amount of methyl *tert*-butyl ether (Fig. 5b and d). For compound **14**, the efficiencies (number of theoretical plates, *N*) for peak 1 are 1200 and 500 using methyl *tert*-butyl ether as an additive versus no additive, respectively. For compound **15**, the efficiency of

Table 2
Retention factor of the first peak (k_1), enantioselectivity (α), and enantioresolution (R_S) of chiral furans separated on the Cyclobond SN and DMP CSPs

Compound no.	k_1	α	R_S	Mobile phase (v/v)
Cyclobond SN CSP				
5[a]	2.11	1.26	1.7	CH_3OH/H_2O = 60/40
9	5.94	1.08	0.6	CH_3OH/H_2O = 60/40
12	1.00	1.06	0.3	CH_3OH/H_2O = 60/40
14	7.55	1.07	0.6	CH_3OH/H_2O = 60/40
21	1.40	1.08	0.6	CH_3OH/H_2O = 60/40
Cyclobond DMP CSP				
5[a]	12.54	1.02	0.3	CH_3OH/H_2O = 60/40
8	3.98	1.06	0.5	CH_3OH/H_2O = 70/30
14	14.36	1.03	0.4	CH_3OH/H_2O = 60/40
17	10.36	1.11	1.5	CH_3OH/H_2O = 70/30

[a] Separation of diastereomers.

Table 3
Retention factor of the first peak (k_1), enantioselectivity (α), and enantioresolution (R_S) of compounds **3**, **7**, and **14** at different pHs of the mobile phase (0.1% triethylamine with pH adjusted by acetic acid)

pH		4			5			6			7			8		
Number	CSP	k_1	α	R_S	k_1	α	R_S	k_1	α	R_S	k_1	α	R_S	k_1	α	R_S
3	AC	1.74	1.14	1.6	2.53	1.15	2.1	1.04	1.19	1.6	0.26	1.35	1.1	0.18	1.50	1.1
7	DM	3.16	1.35	2.0	3.73	1.35	2.1	3.91	1.35	2.0	3.59	1.35	2.1	3.57	1.35	2.1
	RSP	4.14	1.17	1.6	4.19	1.18	1.8	4.20	1.17	1.8	3.93	1.17	1.8	4.02	1.17	1.8
14	RSP	5.95	1.37	3.4	6.92	1.37	3.5	7.23	1.37	3.7	6.74	1.37	3.7	6.88	1.37	3.6
	AC	3.50	1.36	2.4	5.00	1.36	2.7	5.64	1.36	2.8	5.81	1.36	3.1	5.67	1.36	3.0

peak 1 increased from 660 to 3300 with the additive in the mobile phase. Therefore, better efficiency and shorter separation times were achieved, although the enantioselectivity was similar. The methyl *tert*-butyl ether serves as a competitive binding agent for the cyclodextrin cavity, thereby displacing the analyte more readily and effectively than other mobile phase components.

3.3. Effects due to the structure of the individual analyte

The differences in the structures of the compounds greatly affect the enantioseparations of the three groups of analytes listed in Table 1 and Fig. 1. The chiral tetrahydrobenzofurans are the easiest to separate. The Cyclobond CSPs showed enantioselectivity for all 22 of these compounds and baseline separated 15 of them. These same CSPs showed moderate selectivity for the four furochromenes. All four compounds were separated with one providing a baseline separation. The four simple, multiply-substituted furans were the most difficult to separate with the Cyclobond CSPs. Only partial separations of two of these compounds were observed.

3.3.1. Effect of an iodide group

It is well known that halogen substituents have a strong affinity for the cyclodextrin cavity. Therefore, an iodide substituent in the analyte may play an important role in the enantioseparation. For example, the separations of compounds **27** and **30** clearly show the effect of an iodide group in the β-position of the furan ring on the enantioseparation. Compound **27** cannot be separated on any Cyclobond column, but a partial separation of compound **30** was observed on the Cyclobond AC, RSP, and DM CSPs. A comparison of compounds **23** and **25** is more interesting (Fig. 6). The Cyclobond RSP column showed a baseline separation for compound **23**, which has an iodide substituent in the β-position of the furan ring, while no enantioselectivity was observed on the Cyclobond DM and AC columns. Compound **25**, which has no iodide substituent, could be only partial separated on the Cyclobond DM, RSP, and AC CSPs. For compounds **17** and **19**,

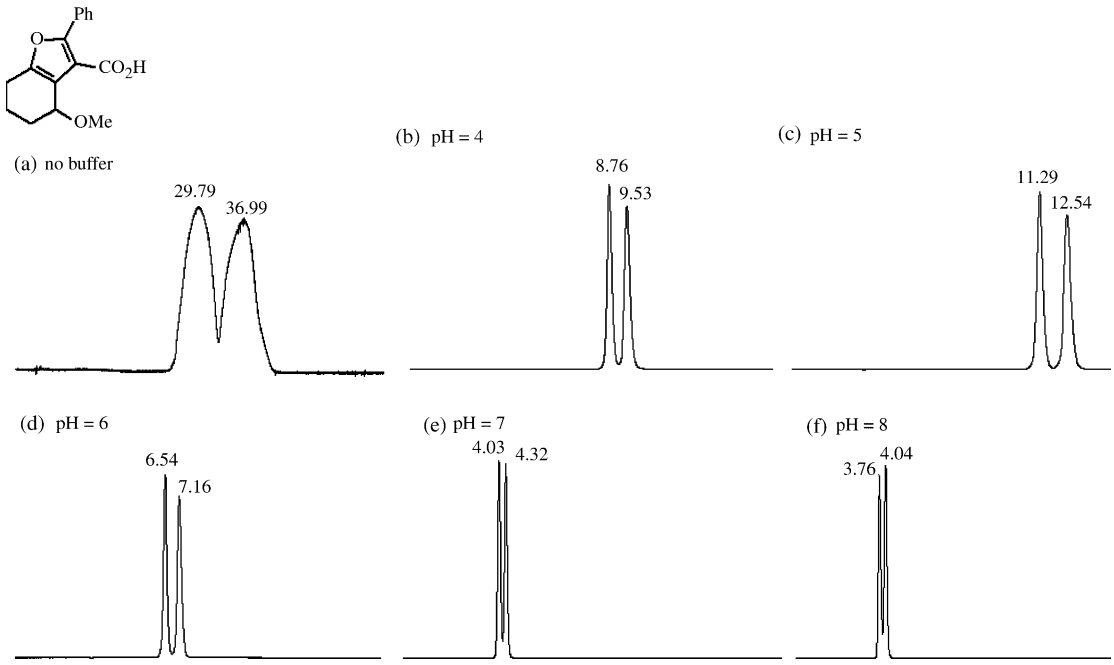


Fig. 4. The pH effect for the enantioseparation of compound **3** on the Cyclobond AC CSP. Mobile phase: (a) CH_3OH/H_2O = 60/40, (b)–(f) were used a mobile phase of CH_3OH/buffer = 60/40 where the buffer was 0.1% triethylamine with different concentrations of acetic acid to adjust the pH values indicated above.

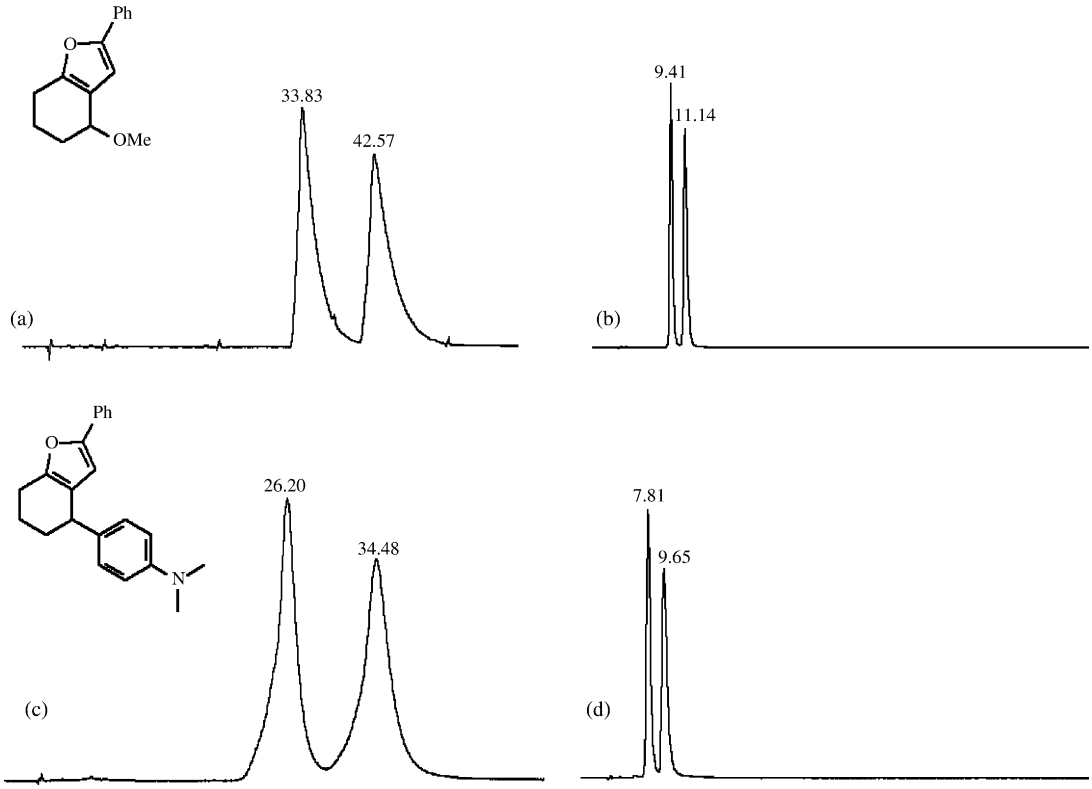


Fig. 5. The effect of 0.5% methyl *tert*-butyl ether in the mobile phase for the separation of compounds **14** and **15**. Chromatograms (a) and (b) were done using the Cyclobond DM CSP. Chromatograms (c) and (d) were done using the Cyclobond AC CSP. The mobile phase composition in each case was as follows: (a) $CH_3OH/H_2O = 40/60$, (b) CH_3OH/H_2O/methyl *tert*-butyl ether = 40/60/0.5, (c) $CH_3OH/H_2O = 50/50$, (d) CH_3OH/H_2O/methyl *tert*-butyl ether = 50/50/0.5. Enantioselectivity α: (a) $\alpha = 1.28$, (b) $\alpha = 1.28$, (c) $\alpha = 1.36$, (d) $\alpha = 1.40$. Number of theoretical plates of the first peak N_1: (a) $N_1 = 660$, (b) $N_1 = 3300$, (c) $N_1 = 500$, (d) $N_1 = 1200$.

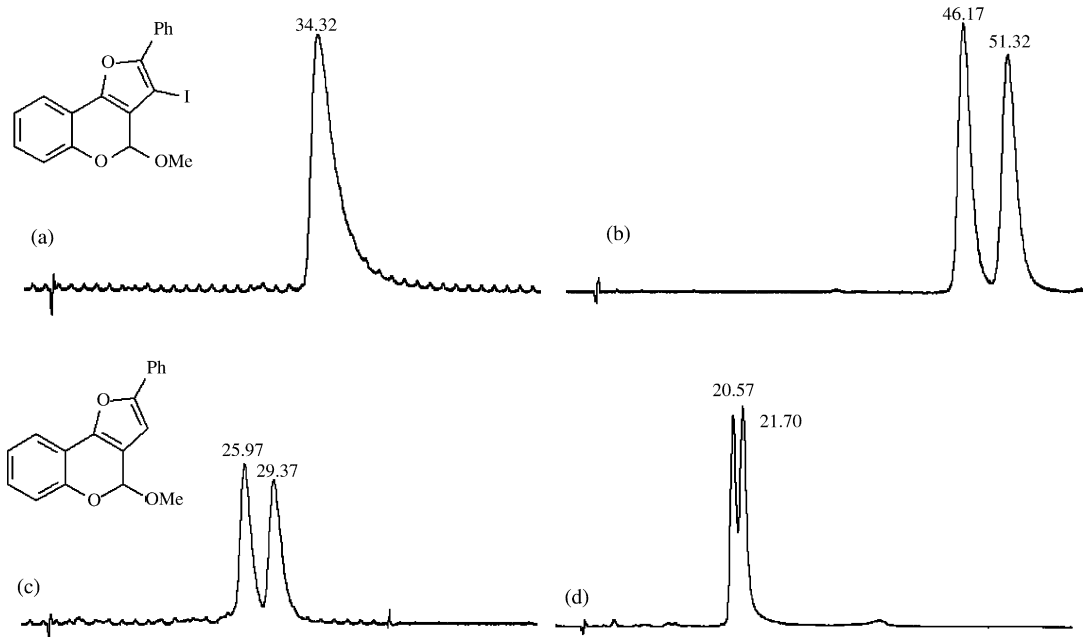


Fig. 6. The iodide effect on the separation for compounds **23** and **25**. Chromatograms (a) and (c) were done using the Cyclobond DM CSP. Chromatograms (b) and (d) were done using the Cyclobond RSP CSP. The mobile phase composition in each chromatogram was as follows: (a) and (c) $CH_3OH/H_2O = 35/65$, (b) $CH_3OH/H_2O = 45/55$, (d) $CH_3OH/H_2O = 50/50$.

the iodide group in compound **19** enhanced the enantioselectivity on the Cyclobond RSP, DM and AC CSPs. However, for compounds **18** and **20**, the enantioselectivity for compound **18** was much better on the Cyclobond DM CSP compared to that of compound **20**. Clearly, the presence of a halogen substituent can either help or hurt an enantiomeric separation depending on its exact location. If the halogen moiety redirects inclusion complexation (by offering a more favorable complexation site) away from the stereogenic center and/or its substituents, it can hurt an enantioselective separation. Conversely, if the presence of a halogen moiety redirects inclusion complexation in such a way that there is enhanced interaction with the substituents from the stereogenic center, the enantioselective separation can be improved.

3.3.2. Steric effects

Steric repulsion plays an important role in chiral recognition for the Cyclobond DM CSP. The separations of compounds **6** and **15** show that an increase in steric bulk near their stereogenic centers improves the separation on the Cyclobond DM CSP. These two compounds have similar structures. The only difference is that compound **15** has a six-membered ring fused to the furan moiety, while compound **6** has a seven-membered ring. The bigger ring in compound **6** produces less retention, but higher enantioselectivity (Fig. 7). A similar trend can be found for compounds **15**, **10**, and **12**. With an increase in the size of the substitutent connected to the chiral center (from a methoxy group, to an allyloxy group to an isopropoxy group), a decrease in retention coupled with an enhancement in the enantioresolution was observed. However, too large an increase in the steric bulk around the chiral center of the analyte can hinder the separation on the Cyclobond DM CSP. For example, compounds **13** and **5**, which have much more bulky substituents attached to the chiral center, could not be resolved on the Cyclobond DM CSP, while they can be separated on the Cyclobond AC and SN CSPs, respectively.

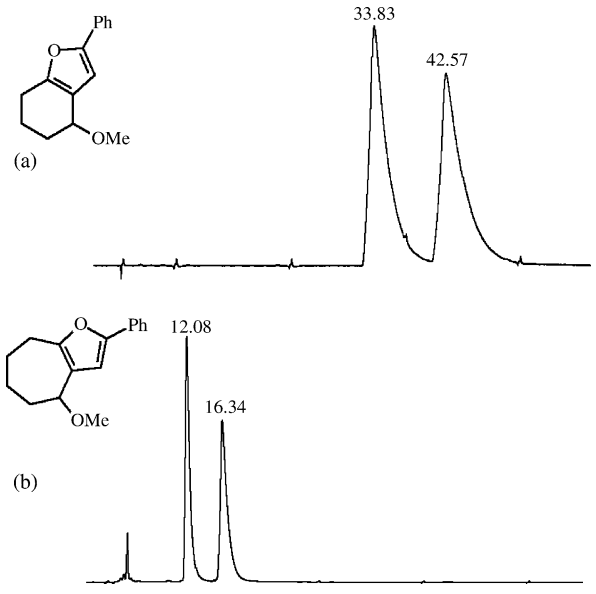


Fig. 7. Steric effect on the separation of compounds **15** and **6** on Cyclobond DM CSP. Mobile phase: $CH_3OH/H_2O = 40/60$. Enantioselectivity α: (a) $\alpha = 1.28$, (b) $\alpha = 1.48$.

3.3.3. Effect of hydrogen bonding groups

Hydrogen bonding interactions greatly affect separations on Cyclobond RSP and AC CSPs. For example, compound **3**, which has a carboxylic acid group (a hydrogen bond donor and acceptor), shows satisfactory enantioseparation on the Cyclobond AC CSP with the methanol/buffer mobile phase. While compound **15**, which has no carboxylic acid group, showed no enantioselectivity on this CSP. Another example is the separation of compounds **14** and **11**. The presence of a tertiary amine group, a much better hydrogen bond acceptor compared to iodine, results in compound **14** being baseline separated on the Cyclobond RSP and AC columns, while no enantioselectivity was observed for compound **11** on these CSPs. Some other compounds with hydrogen bond donor or acceptor groups, such as compounds **2**, **7**, and **13**, also show acceptable enantioseparation on the Cyclobond RSP or AC CSPs.

3.3.4. Effect of substituent geometry

The separations of two pairs of compounds **17**, **18** and **19**, **20** are also interesting. Each pair has similar structures. Both of them have two chiral centers, one of which is the *trans* configuration and the other is the *cis* configuration. The two compounds showed different selectivity on different cyclodextrin CSPs. For the first group, compounds **17** and **18**, Cyclobond RSP and AC CSPs showed better selectivity for the analyte with the *trans* configuration, but the compound with the *cis* configuration was separated better on the Cyclobond DM CSP. For the second group, compounds **19** and **20**, all three non-aromatic derivatized Cyclobond CSPs produced better enantioseparations for the compound with the *trans* configuration than the one with the *cis* configuration. Another interesting example of the effect of geometry is compound **21**. It can be baseline separated on any non-aromatic derivatized Cyclobond CSPs due to its highly rigid fused tricyclic structure.

4. Conclusions

The Cyclobond DM, RSP, and AC CSPs have been shown to be very effective for the enantioselective separation of many chiral, substituted furan derivatives in the reverse phase mode. The nature of the organic modifier has little effect on the enantioseparation. The pH of the mobile phase only affects the separation of the compounds with ionizable groups. The addition of 0.5% methyl *tert*-butyl ether to the mobile phase enhanced the separation for some compounds, which had high α-values, but very poor efficiencies. The nature of the compounds, including the steric bulk, hydrogen bonding ability, and geometry, greatly affects the chiral recognition.

In general, the tetrahydrobenzofurans and furochromenes are better separated than simple substituted furans. The normal phase and polar organic phase are not as effective as the reverse phase mode for the separation of these compounds.

Acknowledgements

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