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Separation performance and recognition mechanism of mono(6-deoxy-imino)-β-cyclodextrins chiral stationary phases in high-performance liquid chromatography

Zhi-Ming Zhou*, Xia Li, Xiao-Ping Chen, Min Fang, Xiao Dong

School of Chemical Engineering and the Environment, Beijing Institute of Technology, Beijing 100081, China

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ABSTRACT

Different substituent groups were introduced onto the rim of β-cyclodextrin through rigid C=N bonds to form a series of imino-modified β-cyclodextrin derivatives: mono(6-deoxy-phenylimino)-β-cyclodextrin (BCD), mono(6-deoxy-isopropylimino)-β-cyclodextrin (YBCD), mono(6-deoxy-*N*-1-phenylethylimino)-β-cyclodextrin (R-,S-BYCD), mono[6-deoxy-*N*-1-(2-hydroxyl)-phenylethylimino]-β-cyclodextrin (R-,S-PGCD), heptakis(2,6-o-diamyl-6-deoxy-phenylimino)-β-cyclodextrin (WBCD), heptakis(2,6-o-diamyl-6-deoxyisopropylimino)-β-cyclodextrin (WYBCD) and heptakis[2,6-o-diamyl-6-deoxy-R-(-)-*N*-1-phenylethylimino)-β-cyclodextrin (WRBYCD). The obtained derivatives were then bonded to silica gel and used in high-performance liquid chromatography (HPLC) as chiral stationary phases (CSPs). The separation performance of these CSPs was examined by separating disubstituted benzenes, amino acids, ferrocene derivatives andchiral aromatic alcohol compounds. Satisfactory separation results were obtained for most of the compounds. The values for selectivity factors can reach up to 8.50 and 8.16 for separating positional isomers and ferrocene derivatives, respectively, and the best resolution was 6.89 for aromatic alcohol derivative separations. Molecular dynamics (MD) simulations were carried out for chiral discrimination of rac-*N*-benzoyl-phenylglycinol on S-PGCD CSP to study the recognition mechanism. MD simulation results show that the average free-energy of interaction is −1304.83 kcal/mol for the L-enantiomer and S-PGCD and −1324.23 kcal/mol for the D-enantiomer and S-PGCD. In the recognition stage, the L-enantiomer moves along the exterior of the cyclodextrin cavity from the wider edge to the narrower edge of cyclodextrin whereas the D-enantiomer moves slightly towards the cavity. The L-enantiomer thus is separated first due to weaker interaction with S-PGCD.

1. Introduction

Cyclodextrins (CDs) were first discovered in 1891 by Villiers [1]. In 1938, Freudenberg and Mayer-Delius [2] experimentally confirmed the macrocyclic structures of CDs. The structures of α- and β-CD were determined in 1942 by X-ray crystallography, and the structure of γ-CD was ascertained in 1948 [3]. CDs [4] are cyclic oligosaccharides consisting of D-glucopyranose units bonded through α-(1,4) glycosidic linkages. The shape of a CD molecule resembles a truncated cone with a cavity with secondary hydroxyl groups at the C-2 and C-3 positions located on the wider edge of the ring, and the primary hydroxyl groups at the C-6 position located on the narrower edge. This makes the external surface of the cavity present a hydrophilic face, and hydroxyl groups on the rim of CD can be easily modified by substituent groups to form various CD derivatives. In contrast, the internal surface of the CD cavity, which consists of glycosidic oxygens and methane protons, is hydrophobic. Due to the unique nature of the structure, CDs are able to form supermolecular systems between other CDs, their derivatives and solutes through van der Waals interactions, hydrophobic interactions, hydrogen bonding, π–π interactions, dipole–dipole interactions and electrostatic interactions. As a result, this feature has attracted great attention in many application fields such as pharmaceutical applications [5–7], chiral separation [8–10], the catalyst industry [11,12], the food industry [13], and molecular imprinting [14,15], artificial enzymes [16–18] and environmental protection [19].

In HPLC separation of positional isomers and enantiomers, the use of β-CD and its derivatives bonded to silica gel as CSPs has proven to be one of the most efficient techniques [10,20–24]. Until 1990, most of the studies [25–30] focused on the preparation of native β-CD CSPs modified by different linkage groups and the separation of positional isomers. As for the enantiomers, the analytes need to get into the cavity of cyclodextrin, and the formation of inclusion complexes played an important role during separation before 1990. CSPs

* Corresponding author. Tel.: +86 10 6891 8982; fax: +86 10 6891 2664.
E-mail address: zzm@bit.edu.cn (Z.-M. Zhou).

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were then mainly utilized in the reverse phase mode. Because the application of native β-CD CSPs was not always satisfactory. Armstrong et al. [31] synthesized peracety-derivatized-β-CD, toluoyl-derivatized-β-CD, 2,6-dimethylphenyl isocyanate-derivatized-β-CD, R-naphthylethyl isocyanate-derivatized-β-CD and s-naphthylethyl isocyanate-derivatized-β-CD in 1990, and first utilized them as chiral stationary phases under the normal phase mode to separate enantiomers. In this way, inclusion complexation was not thought to be necessary for separating enantiomers. For β-CD derivatives, modifiers have important effects on separation efficiency. Currently, substituent group-modified β-CDs can be divided into three types: the hydrophobic, the hydrophilic and the charged groups. Introduction of substituent groups onto the rim of β-CD can change the size of the cavity and form π–π interactions, dipole–dipole interactions and electrostatic interactions, and it can increase hydrogen bonding between hosts and guests. Consequently, this is useful in the separation of more varieties of isomers. For example, Soukup et al. [32] used hydroxypropyl-β-CD CSP to separate coumarin ketone and its derivatives. Ng and co-workers [33,34] synthesized permethylated CD CSP and separated chiral aromatic compounds. Fujimura et al. [35] prepared isocyanate-modified CD CSPs and separated a variety of amino acids. With the development of the chemical industry and the increasing demand of single isomer purification, investigation of novel β-CD derivatives as chiral selectors that can separate a larger number of kinds of isomers has become more and more important.

In our previous work [36], rigid C=N bonds were brought onto β-CD based on the assumption that a rigid structure was essential to obtain good enantioselectivity in asymmetric catalysis. In this work, we have extended our previous study [36–39] and prepared more diverse groups of substituted imino-β-CD derivatives, including mono(6-deoxy-*N*-1-phenylethylimino)-β-cyclodextrin (R-,S-BYCD), mono[6-deoxy-R-(-)-*N*-1-(2-hydroxyl)-phenylethylimino]-β-cyclodextrin (R-PGCD), heptakis(2,6-o-diamyl-6-deoxy-phenylimino)-β-cyclodextrin (WBCD) and heptakis[2,6-o-diamyl-6-deoxy-R-(-)-*N*-1-phenylethylimino)-β-cyclodextrin (WRBYCD). We have used these in HPLC as CSPs through bonding to silica gel. In addition, the influences of different substituent groups on β-CDs on the separation of disubstituted benzenes, amino acids, ferrocene derivatives and chiral aromatic alcohol compounds were compared. It is expected that better separation ability could be achieved by adapting the hydrophobic interactions, π–π, hydrogen bonding, dipolar–dipolar interactions, conformation inductive effects, etc. Furthermore, in order to gain a deeper insight into the recognition mechanism. We also carried out molecular dynamics (MD) simulations on the recognition interactions of N-benzoyl-phenylglycinol enantiomers and S-PGCD.

2. Experimental

2.1. Materials

All stationary phases were obtained from the chiral selector bonded to the surface of 5 μm spherical silica gel, which was heated at 160 °C for 12 h and kept in a desiccator before use. The chiral

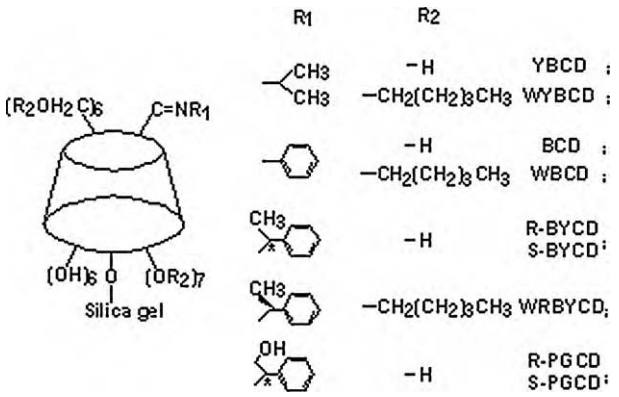


Fig. 1. The structures of nine different CSPs based on imino-substituted β-cyclodextrins. An asterisk denotes the stereogenic center.

selectors used were imino-substituted β-cyclodextrins YBCD, BCD, R-BYCD, S-BYCD, R-PGCD, S-PGCD, WYBCD, WBCD and WRBYCD, and they are shown in Fig. 1. Methanol, acetonitrile, isopropanol, hexane, acetic acid and triethylamine were of HPLC grade. Triethylammonium acetate buffers (TEAA) at the desired pH were prepared by the addition of glacial acetic acid to 1% aqueous triethylamine.

2.2. Preparation of CSPs

All CSPs were synthesized according to the procedure reported previously [36]: one of the hydroxyl groups at the C-6 position of β-CD was oxidized by 2-iodoxybenzoic acid (IBX) to form 6-monoaldehyde-β-CD which then was attacked by different nucleophilic reagent amides to yield a series of imino-substituted β-cyclodextrins: YBCD, WYBCD, BCD, R-,S-BYCD, R-,S-PGCD, WBCD and WRBYCD. Through bonding these β-cyclodextrin derivatives to silica gel, the CSPs with a Schiff base group were prepared. The characteristics of these stationary phases were analyzed by FT-IR spectra and elemental analysis. The data for YBCD, WYBCD and BCD CSPs have been reported in previous articles [36–39], and those of the new ones are listed in Table 1. The concentrations of derivatized β-CDs bonded to silica gel were calculated based on elemental analysis results according to the formula [40]: $\frac{\mu mol}{m^2} = \frac{\%N \times 10^6}{S(1400 \times n_N - \%N \times M_r)}$ where N is nitrogen's percentage in the sample, which is determined by elemental analysis, M_r is the molecular weight of the cyclodextrin derivative, n_N is the number of nitrogen atoms in the chiral selector [41], and S is the special surface area of silica gel, which is 320 m^2/g according to the manufacturer.

2.3. Apparatus

The HPLC system used consisted of two Wellchrom HPLC pumps (K-501), a manual injection valve model (7725i), a Wellchrom spectrophotometer (K-2501) and a dynamic mixing chamber. The mobile phases were filtered through a membrane filter of 0.45 μm pore size and degassed under reduced pressure before use. The wavelength used for detection was 254 nm. In order to avoid the interference from solvent, solvent without solute was analysed

Table 1
The characteristic data for R-,S-BYCD, R-,S-PGCD, WBCD and WRBYCD.

CSPs	IR (KBr, v/cm^{-1})	Elemental analysis	Concentration (mol/m^2)
R-BYCD CSP	3442, 2956, 1702, 1631, 1095, 804, 468	C, 14.52%; H, 2.75%; N, 0.17%	0.45
S-BYCD CSP	3434, 2956, 1702, 1631, 1255, 1095, 802, 463	C, 10.21%; H, 2.01%; N, 0.24%	0.69
R-PGCD CSP	3463, 2942, 1631, 1230, 1089, 800, 460	C, 12.37%; H, 2.24%; N, 0.65%	3.46
S-PGCD CSP	3442, 2949, 1631, 1091, 804, 468	C, 12.12%; H, 2.33%; N, 0.66%	3.59
WBCD CSP	3443, 2952, 1711, 1396, 1095, 803, 464	C, 11.25%; H, 2.43%; N, 0.41%	2.24
WRBYCD CSP	3427, 2963, 1716, 1259, 1095, 803, 464	C, 7.95%; H, 1.82%; N, 0.18%	0.54

Table 2
Chromatographic separation results of positional isomers toluidine, nitrotoluene and dichlorobenzene on BCD, YBCD, R-BYCD, S-BYCD, WBCD, WYBCD and WRBYCD CSPs.

Compound	CSP	k'	α	Elution order	CSP	k'	α	Elution order	CSP	k'	α	Elution order	CSP	k'	α	Elution order
p-toluidine, *m*-toluidine, *o*-toluidine		0.11[a]	1.00[a]			2.61[d]	1.01[d]			3.00[e]	1.03[e]			3.50[e]	1.03[e]	
		0.12[a]	1.09[a]	*p*, *m*, *o*		2.58[d]	1.19[d]	*o*, *m*, *p*		2.91[e]	1.26[e]	*o*, *m*, *p*		3.40[e]	1.29[e]	*o*, *m*, *p*
		0.13[a]	1.08[a]			2.18[d]	1.00[d]			2.31[e]	1.00[e]			2.64[e]	1.00[e]	
		0.18[b]	1.06[b]			4.27[f]	0.99[f]			4.79[f]	1.05[f]			4.83[f]	1.29[f]	
	BCD	0.17[b]	1.00[b]	*m*, *p*, *o*	YBCD	4.30[f]	1.37[f]	*o*, *p*, *m*	R-BYCD	4.56[f]	1.34[f]	*o*, *m*, *p*	WRBYCD	4.85[f]	1.00[f]	*o*, *p*, *m*
		0.21[b]	1.17[b]			3.13[f]	1.00[f]			3.40[f]	1.00[f]			3.74[f]	1.00[f]	
		0.34[c]	1.42[c]			7.06[g]	1.03[g]			10.56[g]	1.36[g]			25.76[g]	1.15[g]	
		2.49[c]	7.32[c]	*o*, *p*, *m*		6.83[g]	1.31[g]	*o*, *m*, *p*		15.54[g]	1.47[g]	*o*, *p*, *m*		22.36[g]	2.31[g]	*o*, *m*, *p*
		0.24[c]	1.00[c]			5.21[g]	1.00[g]			7.77[g]	1.00[g]			9.69[g]	1.00[g]	
		3.69[d]	1.05[d]			2.34[d]	1.00[d]			3.33[e]	1.00[e]					
		2.92[d]	1.00[d]	*m*, *o*, *p*		2.82[d]	1.15[d]	*p*, *m*, *o*		3.91[e]	1.17[e]	*p*, *m*, *o*				
		3.52[d]	1.21[d]			2.44[d]	1.04[d]			3.95[e]	1.01[e]					
		4.69[f]	1.20[f]			2.62[f]	1.18[f]			4.60[f]	1.00[f]					
	WBCD	3.90[f]	1.02[f]	*o*, *m*, *p*	WYBCD	2.71[f]	1.03[f]	*o*, *p*, *m*	S-BYCD	6.02[f]	1.31[f]	*p*, *m*, *o*				
		3.83[f]	1.00[f]			2.23[f]	1.00[f]			6.07[f]	1.01[f]					
		10.92[g]	1.00[g]			7.04[g]	1.49[g]	*o*, *p*, *m*		11.49[g]	1.00[g]					
		6.76[g]	1.62[g]	*o*, *p*, *m*		7.44[g]	1.06[g]			23.82[g]	2.07[g]	*p*, *m*				
		10.92[g]	1.00[g]			4.74[g]	1.00[g]			–	–					
		0.19[a]	1.00[a]			0.87[d]	1.06[d]			0.75[e]	1.00[e]	*o*, *m*, *p*		1.00[e]	1.00[e]	
		0.29[a]	1.53[a]	*o*, *m*, *p*		0.82[d]	1.00[d]	*m*, *o*, *p*		0.92[e]	1.23[e]			1.02[e]	1.02[e]	*o*, *m*, *p*
		0.52[a]														
			1.79[a]			0.89[d]	1.02[d]			0.96[e]	1.05[e]			1.14[e]	1.12[e]	
	BCD	2.84[b]	1.19[b]		YBCD	1.03[f]	1.04[f]		R-BYCD	1.15[f]	1.03[f]		WRBYCD	1.10[f]	1.04[f]	
			8.50[b]	*p*, *m*, *o*				*m*, *o*, *p*				*m*, *o*, *p*				*m*, *o*, *p*
			1.00[b]													
o-nitrotoluene, *m*-nitrotoluene, *p*-nitrotoluene		2.38[b]				0.99[f]	1.00[f]			1.12[f]	1.00[f]			1.06[f]	1.00[f]	
		0.28[b]														
						1.16[f]	1.12[f]			1.31[f]	1.14[f]			1.15[f]	1.05[f]	
		3.43[c]	1.00[c]			1.08[g]	1.04[g]			2.43[g]	1.12[g]			1.36[g]	1.17[g]	
			1.05[c]	*o*, *p*, *m*				*m*, *o*, *p*				*m*, *o*, *p*				*m*, *o*, *p*
			1.13[c]													
		4.06[c]				1.04[g]	1.00[g]			2.17[g]	1.00[g]			1.16[g]	1.00[g]	
		3.86[c]														
						1.20[g]	1.11[g]			2.77[g]	1.14[g]			1.42[g]	1.05[g]	
		1.12[d]	1.01[d]			1.00[d]	1.00[d]			1.21[e]	1.00[e]					
		1.11[d]	1.00[d]	*m*, *o*, *p*		1.01[d]	1.01[d]	*o*, *m*, *p*		1.23[e]	1.01[e]	*o*, *p*, *m*				
		1.24[d]	1.10[d]			1.12[d]	1.11[d]			1.38[e]	1.12[e]					
		1.31[f]	1.02[f]			0.90[f]	1.01[f]			1.49[f]	1.00[f]					
	WBCD	1.29[f]	1.00[f]	*m*, *o*, *p*	WYBCD	0.89[f]	1.00[f]	*m*, *o*, *p*	S-BYCD	–	–	*o*, *p*				
		1.41[f]	1.07[f]			0.95[f]	1.06[f]			1.68[f]	1.13[f]					
		1.39[g]	1.00[g]			1.60[g]	1.04[g]			3.09[g]	1.00[g]					
		1.65[g]	1.02[g]	*o*, *p*, *m*		1.39[g]	1.00[g]	*m*, *p*, *o*		3.11[g]	1.01[g]	*o*, *p*, *m*				
		1.62[g]	1.17[g]			1.54[g]	1.11[g]			3.26[g]	1.05[g]					
		1.31[a]	1.00[a]			–	–			0.44[e]	1.00[e]			0.41[e]	1.00[e]	
			1.24[a]	*o*, *p*, *m*								*o*, *p*, *m*				*o*, *p*, *m*
			1.37[a]													
		1.63[a]								0.45[e]	1.01[e]			0.42[e]	1.02[e]	
	BCD	2.24[a]			YBCD				R-BYCD				WRBYCD			
										0.49[e]	1.10[e]			0.50[e]	1.21[e]	
		6.41[b]	1.01[b]			0.46[f]	1.02[f]			0.52[f]	1.01[f]			0.51[f]	1.00[f]	
			1.00[b]	*p*, *m*, *o*				*m*, *o*, *p*				*o*, *m*, *p*				*o*, *p*, *m*
			1.06[b]													
o-dichlorobenzene, *p*-dichlorobenzene, *m*-dichlorobenzene		5.96[b]				0.47[f]	1.02[f]			0.54[f]	1.03[f]			0.53[f]	1.03[f]	
		6.34[b]														
						0.45[f]	1.00[f]			0.52[f]	1.00[f]			0.79[f]	1.51[f]	

Table 2 (*Continued*)

Compound	CSP	k'	α	Elution order	CSP	k'	α	Elution order	CSP	k'	α	Elution order	CSP	k'	α	Elution order
		25.61[c]	1.00[c]			0.51[g]	1.08[g]			0.72[g]	1.00[g]			0.75[g]	1.00[g]	
		–	–	–		0.60[g]	1.18[g]	*m*, *o*, *p*		0.75[g]	1.04[g]	*o*, *p*, *m*		0.75[g]	1.00[g]	*o*, *p*, *m*
		–	–			0.47[g]	1.00[g]			1.00[g]	1.33[g]			0.79[g]	1.06[g]	
		0.53[d]	1.04[d]			0.54[d]	1.13[d]			0.44[e]	1.00[e]					
		0.51[d]	1.00[d]	*p*, *o*, *m*		0.48[d]	1.00[d]	*p*, *m*, *o*		0.51[e]	1.17[e]	*o*, *p*, *m*				
		0.56[d]	1.06[d]			0.48[d]	1.00[d]			0.99[e]	1.94[e]					
		0.69[f]	1.00[f]			0.49[f]	1.04[f]			0.44[f]	1.00[f]					
	WBCD	0.69[f]	1.03[f]	*m*, *o*, *p*	WYBCD	0.50[f]	1.02[f]	*m*, *o*, *p*	S-BYCD	0.52[f]	1.18[f]	*o*, *p*, *m*				
		0.67[f]	1.00[f]			0.47[f]	1.00[f]			1.17[f]	2.25[f]					
		0.78[g]	1.03[g]			0.63[g]	1.03[g]			0.81[g]	1.12[g]					
		0.74[g]	1.00[g]	*p*, *m*, *o*		0.61[g]	1.00[g]	*p*, *o*, *m*		1.14[g]	1.41[g]	*m*, *o*, *p*				
		0.76[g]	1.03[g]			0.65[g]	1.03[g]			0.73[g]	1.00[g]					

Separation conditions: flow rate, 0.6 ml/min; detection, 254 nm.
[a] Mobile phase composition (v/v), acetonitrile/water (40/60).
[b] Mobile phase composition (v/v), acetonitrile/water (20/80).
[c] Mobile phase composition (v/v), acetonitrile/water (10/90).
[d] Mobile phase composition (v/v), isopropanol/hexane (15/85).
[e] Mobile phase composition (v/v), isopropanol/hexane (10/90).
[f] Mobile phase composition (v/v), isopropanol/hexane (5/95).
[g] Mobile phase composition (v/v), isopropanol/hexane (0/100).

before injecting samples, herein, the solvent used for dissolving solutes is methanol. The simulations were carried out using the Discover program package with the COMPASS force field on a Dell 1800 workstation.

2.4. Column evaluation

The BCD, YBCD, R-,S-PGCD, R-,S-BYCD, WBCD, WYBCD and WRBYCD CSPs were slurry-packed into 150 mm × 4.6 mm i.d. stainless-steel LC columns. The columns of BCD, YBCD, R-PGCD and S-PGCD were evaluated in the reverse phase mode using acetonitrile-water and methanol-water as the mobile phase. The columns of R-BYCD, S-BYCD, WBCD, WYBCD and WRBYCD CSPs were evaluated in the normal phase mode using isopropanol-hexane as mobile phases. The flow rate of the mobile phase was 0.6 ml/min. The analytes were benzene, toluene, dimethylbenzene, phthalic acid and resorcin. The columns gave an efficiency of 2×10^4 to 4×10^4 P/m.

3. Results and discussion

3.1. Chromatographic data and conditions

HPLC chromatographic data are calculated through the following equations. The time of the first observable disturbance of baseline is the dead time (t_0), which is the time for the mobile phase to pass through the column and relates to the efficiency of the column and the height of theoretical plates (H). It is estimated using the peak of refractive index from the injection solvent on each CSP. Two or three main peaks in the chromatographic schemes are thought as isomers of analyte, and corresponding times are the retention time (t_R) of each isomer. The retention factor (k') is calculated through the equation $k' = (t_R - t_0)/t_0$. The selectivity factor (α) and resolution factor (R_S) are calculated using the equations $\alpha = k'_2/k'_1 = (t_{R2} - t_0)/(t_{R1} - t_0)$ and $R_S = 2 \times (t_{R2} - t_{R1})/(W_1 + W_2)$, respectively, which are used to describe chromatographic separation of the isomers. t_{R1} and t_{R1} stand for the retention times of the second and first isomers, respectively, and the corresponding base peak widths are described by W_1 and W_2.

The separation of positional isomers, chiral amino acids, ferrocene derivatives and some chiral aromatic alcohol compounds was studied on the above nine CDs columns at room temperature, and the mobile phase compositions and flow rate confirmed by experiment were all optimizedat.

3.2. Separation of positional isomers of disubstituted benzenes

The separation of positional isomers is always utilized to test the performance of β-CD columns. In the case of nitroaniline isomers, if p-nitroaniline is eluted first instead of last, it indicates that the β-CD loading is very low. In contrast, β-CD columns will have high separation performance. Herein, the separation results of the positional isomers toluidine, nitrotoluene and dichlorobenzene on seven different cyclodextrin-based CSPs in the reserve phase mode and normal phase mode are shown in Table 2. The retention behavior of nitroaniline isomers on YBCD, WYBCD, R-BYCD, S-BYCD and WRBYCD CSPs were shown in Fig. 2. Good performance of these β-CD derivatives columns can be achieved.

From the data summarized in the Table 2, it can be seen that the retention of three positional isomers increased with decreasing the content of acetonitrile in mixtures with water in the reverse phase mode on BCD CSP. Because it is known that decreasing the content of acetonitrile leads to an increase of solvent polarity, less solvent molecules get into the hydrophobic cavity of CD. In this way, hydrophobic interactions between the host and guest are

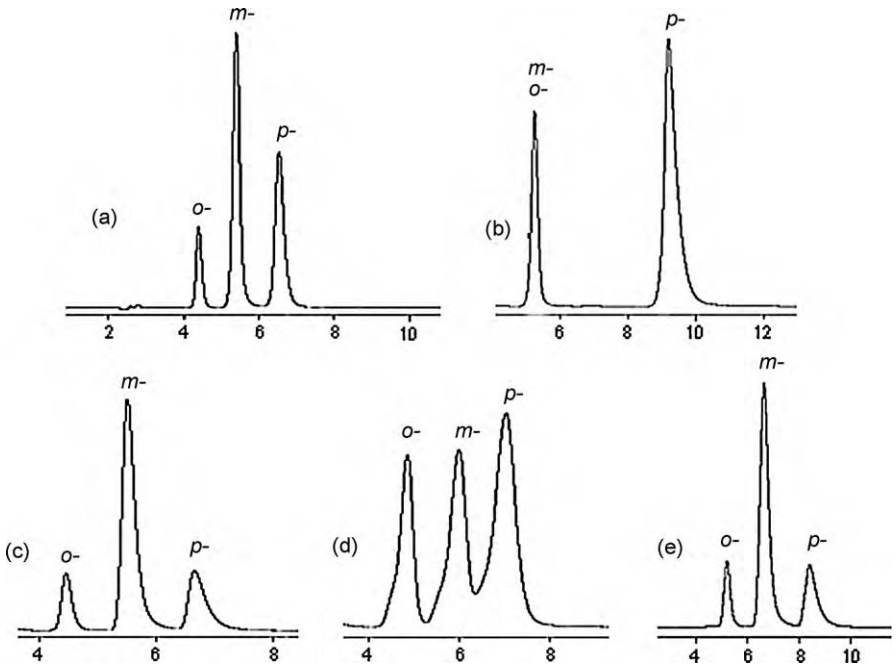


Fig. 2. Separation of nitrotoluene isomers on YBCD CSP (a), WYBCD CSP (b), R-BYCD CSP (c), S-BYCD CSP (d) and WRBYCD CSP (e). Separation conditions: flow rate, 0.6 ml/min; detection, 254 nm; mobile phase composition (v/v): (a) isopropanol/hexane (70/30); (b) isopropanol/hexane (50/50); (c) isopropanol/hexane (30/70); (d) isopropanol/hexane (70/30); (e) isopropanol/hexane (70/30).

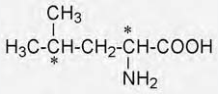
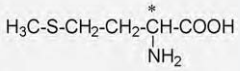
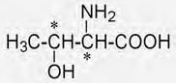
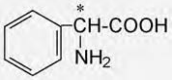
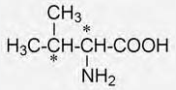
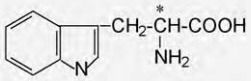
increased. At a constant ratio of acetonitrile-water, the value order of k' is toluidine < nitrotoluene < dichlorobenzene. This is because the electron-donor groups increase the electronic density of the benzene ring and strengthen π–π interaction with the benzene ring on BCD. The retention of chlorine-substituted benzene was larger than amido and nitryl-substituted benzenes on the BCD CSP column. Nitryl-substituted benzene has dipole-dipole interactions with BCD besides the π–π interactions, and therefore, its value of k' is higher than that of amido-substituted benzene. Under the normal phase mode, the retention of the three positional isomers increased with decreasing isopropanol content in its mixtures with hexane on YBCD, R-BYCD, S-BYCD, WBCD, WYBCD or WRBYCD CSPs. Reasons for this are relevant to interactions between solvent and solutes. Solvent polarity decreased with the decrease of the content of isopropanol, and thus interactions were weakened between solvent and solutes. At a constant ratio of isopropanol-hexane, the value order of k' is toluidine > nitrotoluene > dichlorobenzene, in contrast with that on BCD in the reverse phase mode. Thus hydrogen bonding between the solutes and the CD CSPs plays an important role in separation. The retentions of the three positional isomers on the WBCD CSP were greater than that on the WYBCD CSP. This might be ascribed to π–π interactions between solutes and the benzene ring on WBCD. The performance of the YBCD and WYBCD columns was almost identical in separating these compounds. The separation of the three positional isomers of disubstituted benzenes on R-BYCD CSP were better than that on S-BYCD CSP. This result implies that the steric configuration of R-BYCD is more suitable for the separation of positional isomers. The higher values of k' of disubstituted benzene isomers on WRBYCD CSP than that on RBYCD CSP suggest that alkyl groups could increase the interactions between solutes and WRBYCD.

3.3. Separation of amino acids

Amino acids play a major role in living systems as biologically active compounds. Most of them are chiral and have different effects on organisms. In the human body, L-amino acids are beneficial and absorbed easily. D-amino acids, however, usually cannot be metabolized and will be mostly excreted in the urine. Furthermore, D-amino acids found in fermented foods and ripened cheeses probably are of bacterial origin [42]. Thus, there is great importance for the separation of amino acids enantiomers.

Native cyclodextrins and their derivatives bonded to silica gel stationary phases have widely been applied to separate amino acids enantiomers. In our previous work, the retention behavior of the six amino acids leucine, threonine, valine,methionine, phenylalanine and tryptophan on YBCD and WYBCD CSPs at different pHs using acetonitrile-TEAA as the mobile phase was reported [36]. The previous separation data showed that the enantioselectivity of these compounds were best at pH 7.11 on the YBCD column and at pH 5.11 on the WYBCD column. To assess the enantioseparation performance of aromatic, single alkyl and multi-alkyl-substituted mono-6-imine-β-CD CSPs further, the separation data of leucine, threonine, valine, methionine, phenylalanine and tryptophan enantiomers at pH 7.11 on BCD and YBCD CSPs and at pH 5.11 on WYBCD CSP are presented in Table 3. Better separations of leucine, threonine and valine were obtained on BCD and WYBCD CSPs than on the YBCD CSP. Besides dipole-dipole and hydrophobic interactions between solutes and CSPs, benzene ring substituted imine-β-CD increased π–π interactions with solutes. Amyl-substituted β-CD partially covered the mouth of the CD cavity, and the suitable structures of leucine, threonine and valine allow them to enter the cavity of substituted CD more easily as hydrophobic interactions were strengthened. This strengthened their retentions. In the separation, the retention times of the L-amino acids were shorter than those of D-amino acids isomers. This might be ascribed to the stronger interactions between D-amino acids and CD caused by induced conformations. Phenylalanine and tryptophan, however, were not separated successfully on the three CDs columns. It is possible that the steric hindrance of phenylalanine and tryptophan blocks the formation of inclusion complexes with CDs and limits chiral recognition of C3,C5 in the cyclodextrin cavity.

Table 3
The enantioseparation results of amino acids leucine, threonine, valine, methionine, phenylalanine and tryptophan on BCD, YBCD and WYBCD CSPs. Separation conditions: flow rate, 0.6 ml/min; mobile phase composition (v/v), acetonitrile/TEAA (10/90); UV detector, 254 nm. An asterisk denotes thestereogenic center.

Compound	Structure	CSP	k'	α	R_s	Compound	Structure	CSP	k'	α	R_s
Leucine		BCD[a]	1.05 1.27	1.21	1.93	Methionine		BCD[a]	1.35 1.36	1.01	–
		YBCD[a]	1.32 1.47	1.11	1.27			YBCD[a]	2.25 2.26	1.00	–
		WYBCD[b]	1.62 1.87	1.15	1.80			WYBCD[b]	1.62 1.88	1.16	1.71
Threonine		BCD[a]	1.04 1.25	1.20	1.84	Phenylalanine		BCD[a]	0.59 0.63	1.071	–
		YBCD[a]	1.30 1.44	1.11	1.20			YBCD[a]	0.77 0.79	1.02	–
		WYBCD[b]	1.61 1.87	1.16	1.88			WYBCD[b]	0.54 0.55	1.01	–
Valine		BCD[a]	1.04 1.25	1.20	1.85	Tryptophan		BCD[a]	1.54 1.65	1.07	–
		YBCD[a]	1.30 1.45	1.12	1.26			YBCD[a]	1.74 1.81	1.04	–
		WYBCD[b]	1.66 1.90	1.15	1.63			WYBCD[b]	1.08 1.08	1.00	–

[a] pH 7.11.
[b] pH 5.11.

3.4. Separation of ferrocene derivatives

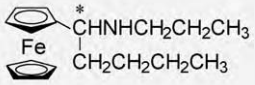
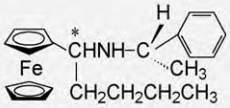
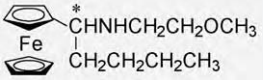
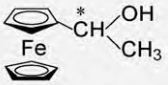
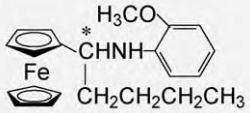
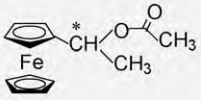
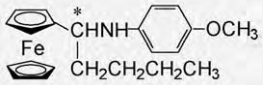
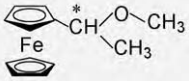
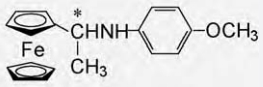
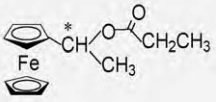
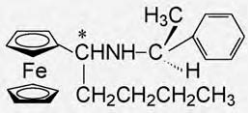
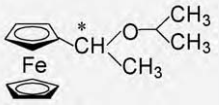
After ferrocene was discovered in 1951, many derivatives were synthesized and characterized that have attracted much attention because of their fascinating sandwich structures and different derivatized groups. They have been applied in many fields of chemistry such as asymmetric synthesis as catalysts [43], electrochemistry as sensors [38], etc. For example, in an asymmetric reaction, the performance of a catalyst not only depends on the degree of the catalyst matching with the substrate, but also closely relates to the optical purity of the ligand. Thus, the chiral separation and qualitative measurement of the ligand play an important role in a successful asymmetric catalysis. In 1994, Takeuchi and Miwa [44] separated some ferrocenylethanol enantiomers using β-CD as mobile phase additive. Mayr et al. [45] separated some chiral ferrocene derivatives using a β-cyclodextrin-based polymer as a chiral selector in 2002, but the results were not so satisfactory. Thus, the successful separation of ferrocene derivatives is still needed.

Herein, we report the separation results of twelve ferrocene derivatives on R-BYCD, S-BYCD, WRBYCD, R-PGCD and S-PGCD CSPs. The separation data are summarized in Table 4. The values ranging from 1.07 to 8.16 imply a good separation of these compounds. Better enantioselectivities for compounds **4.1** and **4.2** were obtained on the S-BYCD column than on the R-BYCD column, but the enantioselectivitives of compounds **4.3, 4.4** and **4.5** displayed the opposite result. This might be due to conformation inductive effects between analytes substituted by different groups and CDs. S-BYCD CSP is more suitable for separating alkyl-substituted ferrocene amine. The enantioselectivities of compounds **4.1** and **4.2** were higher than compounds **4.3**, **4.4** and **4.5** due to the greater steric hindrance of the methoxyphenyl group over the alkyl chain, which blocks the approach of the chiral center of the solute to the CD. The retention capacities of compounds **4.3**, **4.4** and **4.5**, however, on the three CSPs were all better than for compounds **4.1** and **4.2**. This is because of different π–π interactions between the benzene rings of solutes and the CDs. Compound **4.6** afforded better enantioseparation on the S-BYCD column, and compound **4.7** afforded better enantioseparation on the R-BYCD column. This might be ascribed to different conformations of carbon atoms connected on the benzene ring. Comparing the separation results of the analytes on the R-BYCD CSP column with WRBYCD CSP column, it is observed that multiamyl groups substituted on the CD have little effect on the enantioseparation of these compounds, which indicates inclusion complexation cannot always play a major role in the chiral recognition. The separation performance of the R-PGCD column was compared with the S-PGCD column by separating compounds **4.8**–**4.12**. The results show that hydroxyl and carboxyl modified ferrocenes are separated preferably on the R-PGCD column. Apparently, hydroxyl and carboxyl groups could increase hydrogen bonding and dipole-dipole interactions between the solutes and the β-CD derivatives, and therefore, high retentions of these compounds were obtained.

3.5. Separation of chiral aromatic alcohol compounds

Chiral aromatic alcohols are important structural units and are physiologically active compounds in many natural organic compounds. They are important building blocks in synthesizing many active pharmaceuticals and catalysts [46]. The chiral separation of aromatic alcohols has great significance in many areas such as pharmaceuticals, perfumery, vitamins and the synthetic fiber chemical industries [47,48]. Table 5 shows the enantioseparation data for compounds **5.1**–**5.14** on the R-BYCD, S-BYCD, WRBYCD, R-PGCD and S-PGCD columns. Most of these chiral compounds reached baseline separation on these CSPs, except for compounds **5.3** and **5.4** on the S-BYCD CSP and compound **5.12** on both the R-PGCD and S-PGCD CSPs columns. The resolution of compounds **5.1** and **5.2** was better on the WRBYCD column than on the RBYCD column, although their retentions decreased. This might be ascribed to the decreased hydrogen bonding interactions between hydroxyls on the solutes and those on the rim of CD on which most of the hydroxyls were substituted with amyl groups. Compounds **5.3** and **5.4** cannot be separated on S-BYCD CSP, and their resolution was lower on WRBYCD CSP compared to R-BYCD CSP, which indicates that S-BYCD CSP is the most sensitive in separating the two compounds, because of the steric hindrance of the pyridine group that blocks the stereogenic center of the solutes approaching the CD. It is clearly observed that the retentions of compounds **5.1** and

Table 4
The separation data for ferrocene derivatives on R-BYCD, S-BYCD, WRBYCD, R-PGCD and S-PGCD CSPs.

Compound	Structure	CSP	k'	α	Compound	Structure	CSP	k'	α
4.1		R-BYCD[a]	1.39 1.77	1.27	4.7		R-BYCD[b]	0.16 0.39	2.43
		S-BYCD[b]	0.13 0.68	5.26			S-BYCD[b]	0.50 0.98	1.96
		WRBYCD[b]	0.13 0.39	3.00			WRBYCD[b]	0.16 0.61	3.81
4.2		R-BYCD[b]	0.12 0.37	3.09	4.8		S-PGCD[c]	16.09 17.36	1.08
		S-BYCD[b]	0.15 0.70	4.69			R-PGCD[f]	13.17 15.09	1.10
		WRBYCD[b]	0.18 0.53	2.96					
4.3		R-BYCD[b]	1.80 2.72	1.51	4.9		S-PGCD[c]	17.18 18.88	1.10
		S-BYCD[b]	5.47 7.06	1.29			R-PGCD[f]	14.53 16.37	1.13
		WRBYCD[b]	4.64 6.22	1.34					
4.4		R-BYCD[b]	1.13 1.77	1.57	4.10		S-PGCD[e]	5.86 6.47	1.10
		S-BYCD[b]	3.34 4.68	1.40			R-PGCD[f]	15.06 17.14	1.14
		WRBYCD[b]	2.66 3.62	1.36					
4.5		R-BYCD[b]	0.88 1.25	1.42	4.11		S-PGCD[d]	6.97 7.48	1.07
		S-BYCD[b]	3.67 4.44	1.21			R-PGCD[f]	11.53 12.96	1.12
		WRBYCD[b]	1.21 1.70	1.41					
4.6		R-BYCD[b]	0.12 0.38	3.17	4.12		S-PGCD[d]	7.24 7.90	1.09
		S-BYCD[b]	0.12 0.98	8.16			R-PGCD[f]	12.29 13.85	1.13
		WRBYCD[b]	0.19 0.61	3.21					

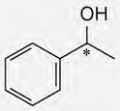
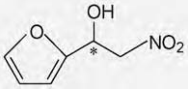
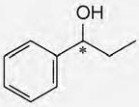
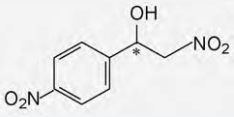
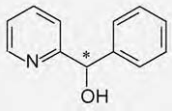
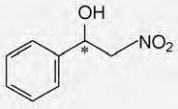
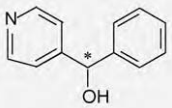
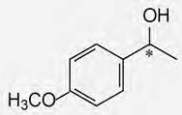
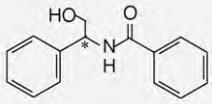
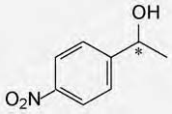
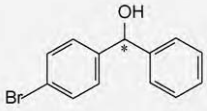
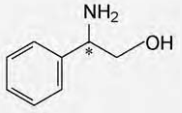
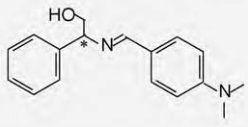
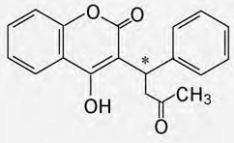
Separation conditions: pH 6.0; detection, 254 nm. An asterisk denotes the stereogenic center.
[a] Flow rate, 0.3 ml/min; mobile phase composition (v/v), acetonitrile/TEAA (10/90).
[b] Flow rate, 0.6 ml/min; mobile phase composition (v/v), acetonitrile/TEAA (30/70).
[c] Flow rate, 0.6 ml/min; mobile phase composition (v/v), acetonitrile/water (30/70).
[d] Flow rate, 0.6 ml/min; mobile phase composition (v/v), acetonitrile/water (40/60).
[e] Flow rate, 0.6 ml/min; mobile phase composition (v/v), acetonitrile/water (45/55).
[f] Flow rate, 0.6 ml/min; mobile phase composition (v/v), acetonitrile/water (35/65).

5.2 were higher than those of **5.3** and **5.4** on these three columns. This is likely because the hydrophobic interactions are stronger between CDs and compounds **5.1** and **5.2** than **5.3** and **5.4**. The separation results of compounds **5.5**–**5.14,** except for **5.12** on the R-PGCD and S-PGCD CSPs show that the former was more suitable for separating these chiral compounds because the configuration of R-(-)-phenylglycinol matches better with the derivatized CD.

3.6. Molecular dynamics (MD) simulations

With the development of computer science, computational calculations have become an effective method to investigate the chiral recognition mechanism, and this us has gained attention over time. In contrast to experimental methods, computational calculations could reproduce various ensembles for the enantioselective instantaneous conformations between the guest enantiomer and host cyclodextrin at the molecular level, and they can save time and resources in understanding the detailed enantiodiscriminative mechanism. In this work, molecular dynamics (MD) simulations were applied to investigate the chiral recognition between rac-*N*-benzoyl-phenylglycinol and S-PGCD. The model parameters for the building blocks are given in Table 6. After reaching the equilibrium of the S-PGCD/water/methanol system, a single N-benzoyl-phenylglycinol enantiomer was introduced into the system and run in the regular way. Fig. 3 presents the optimized conformation of S-PGCD, L-*N*-benzoyl-phenylglycinol and S-PGCD

Table 5
The separation data of fifteen enantiomers on R-BYCD, S-BYCD, WRBYCD, R-PGCD and S-PGCD CSPs.

Number	Structure	CSP	k'	α	R_s	Number	Structure	CSP	k'	α	R_s
5.1		R-BYCD[a]	0.40 0.80	1.99	1.14	5.8		R-PGCD[c]	1.39 1.65	1.19	2.12
		S-BYCD[a]	0.32 0.95	2.98	1.98			S-PGCD[c]	1.52 1.73	1.14	1.71
		WRBYCD[a]	0.35 1.09	3.12	2.89						
5.2		R-BYCD[a]	0.39 0.94	2.42	1.43	5.9		R-PGCD[c]	1.42 1.83	1.29	2.50
		S-BYCD[a]	0.48 1.15	2.39	1.33			S-PGCD[c]	1.54 1.86	1.21	1.98
		WRBYCD[a]	0.34 1.34	3.95	3.29						
		R-PGCD[c]	1.69 2.92	1.73	4.43						
		S-PGCD[c]	1.81 2.41	1.33	2.32						
5.3		R-BYCD[a]	0.19 0.46	2.43	1.45	5.10		R-PGCD[c]	1.38 1.66	1.20	2.00
		S-BYCD[a]	0.19	–	–			S-PGCD[c]	1.50 1.73	1.15	1.70
		WRBYCD[a]	0.31 0.49	1.59	1.09						
5.4		R-BYCD[a]	0.17 0.40	2.33	1.56	5.11		R-PGCD[c]	1.25 1.73	1.38	3.53
		S-BYCD[a]	0.18 0.37	2.06	0.77			S-PGCD[c]	1.50 1.80	1.20	1.84
5.5		R-PGCD[b]	3.10 8.53	2.75	6.89	5.12		R-PGCD[c]	1.53 1.53	1.00	–
		S-PGCD[b]	2.84 6.42	2.26	6.19			S-PGCD[c]	1.84 1.84	1.00	–
5.6		R-PGCD[b]	3.12 5.24	1.68	4.58	5.13		R-PGCD[c]	1.83 2.12	1.16	1.96
		S-PGCD[b]	2.81 4.24	1.51	4.08			S-PGCD[c]	1.66 1.84	1.11	1.04
5.7		R-PGCD[b]	3.76 5.53	1.47	3.77	5.14		R-PGCD[c]	1.35 1.63	1.21	1.61
		S-PGCD[b]	3.68 4.16	1.13	1.10			S-PGCD[c]	1.51 1.74	1.15	1.02

Separation conditions: flow rate, 0.6 ml/min; detection, 254 nm. An asterisk denotes the stereogenic center.
[a] Mobile phase composition (v/v), acetonitrile/TEAA (10/90); pH 3.5.
[b] Mobile phase composition (v/v), methanol/water (50/50).
[c] Mobile phase composition (v/v), acetonitrile/methanol/acetic acid/triethylamine (480/20/1/1).

complex, and D-*N*-benzoyl-phenylglycinol and S-PGCD complex in MD simulations. It shows that the benzene ring of the substituent group on S-PGCD covered the narrower top of β-CD cavity before injecting N-benzoyl-phenylglycinol enantiomer. After adding the single enantiomer to the system, L-*N*-benzoyl-phenylglycinol moved continuously from the wider edge to the narrower edge of CD along the exterior of the cavity, and the complex is basically stable at 1000 ps. Clearly, the hydrogen bonding and π–π interactions between L-*N*-benzoyl-phenylglycinol and derivatized S-PGCD instead of inclusion complexation play a major role in the chiral recognition. However, D-*N*-benzoyl-phenylglycinol was always located at the wider edge of cyclodextrin and a complex was formed through the hydrogen bonding interactions between the solute and the secondary hydroxyl groups on the rim of CD. It can be seen from Fig. 3, for both cases, that the substituent group of the S-PGCD derivative was removed from the top of cavity to the edge while the enantiomers were approaching. D-*N*-benzoyl-phenylglycinol penetrated slightly

Table 6
The model parameters of the building block.

Parameter	Value of parameter
Composition of model	Numbers: methanol (210), imino-substituted β-CD (1), analyte (1) and water (700)
Temperature	298 K
Density	0.9 g cm^{-3}
Length of model	33.61 Å
Ensemble	NPT
Number of steps	5000
Time step	1.0 fs
Dynamics time	5.0 ps
Frame output every	1000
Thermostat	Nose
Barostat	Anderson
Ensemble	NPT

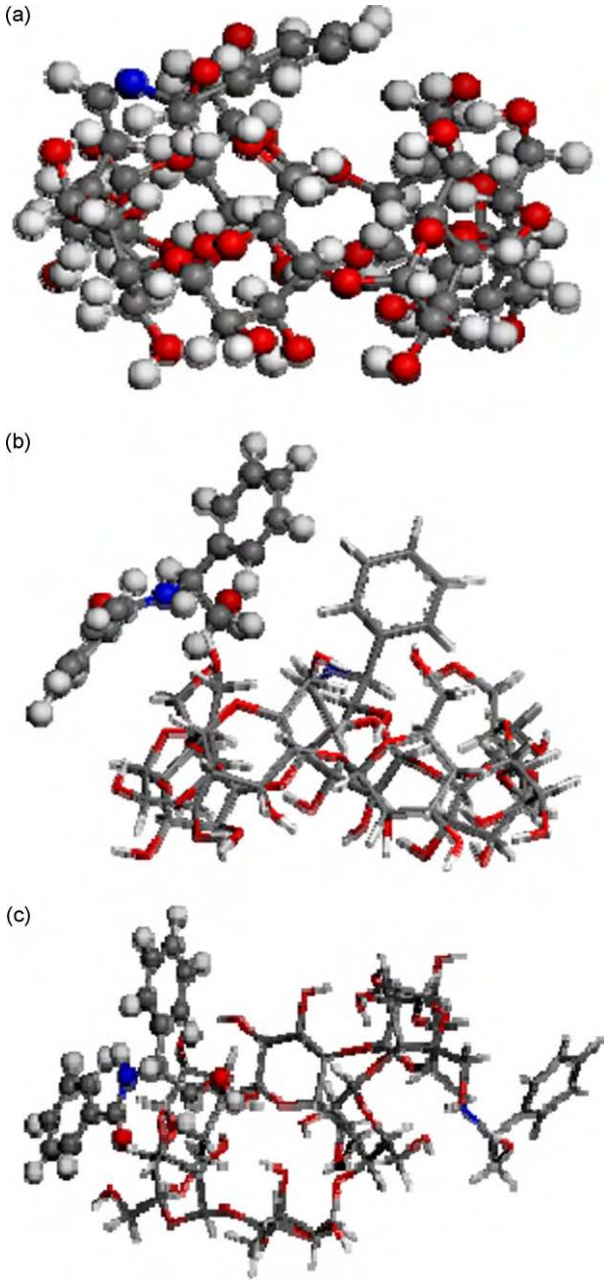


Fig. 3. Side view of energy-minimized structures of the S-PGCD (a), L-*N*-benzoyl-phenylglycinol and S-PGCD complex (b) and D-*N*-benzoyl-phenylglycinol and the S-PGCD complex (c) at 1000 ps in MD simulations.

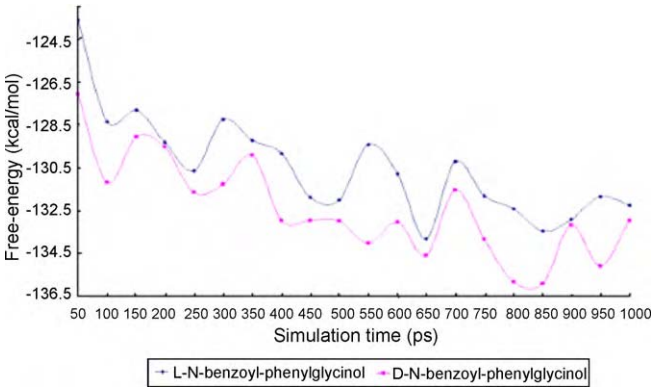


Fig. 4. The free-energy of L- and D-*N*-benzoyl-phenylglycinol/S-PGCD varying with simulation time in 0–1000 ps.

into the CD cavity, as opposed to the L-enantiomer. The variation of free-energy of L- and D-*N*-benzoyl-phenylglycinol/S-PGCD with simulation time is shown in Fig. 4. The average free-energies of L-*N*-benzoyl-phenylglycinol and D-*N*-benzoyl-phenylglycinol are −1304.83 kcal/mol and −1324.23 kcal/mol, respectively. As it is known, the lower the energy, the stronger the interaction, and vice versa. The phenomenon observed above reasonably accords with the experimental separation results that L-*N*-benzoyl-phenylglycinol, having weaker interactions with S-PGCD, is separated before the D-enantiomer, having stronger interactions.

4. Conclusion

In this study, the majority of chiral stationary phases prepared with rigid imino-β-CDs substituted by different groups exhibited high efficiency in the separation of the analytes examined: disubstituted benzenes, amino acids, ferrocene derivatives and chiral aromatic alcohol compounds. It has been shown that the structures of the analytes and the organic modifiers on CDs have excellent effects on the separation. Multi-alkyl substitutions on β-CDs could change the size of the internal cavity, which could enhance the separation of the adapted analytes. The enantioselectivity of different solutes on R-BYCD, S-BYCD, R-PGCD and S-PGCD suggested that the R-configuration matched with CD better than the S-configuration, and thus more satisfactory separation results could be obtained for most of the analytes tested. Through MD simulations, it is observed that the recognition process of β-CD derivatives with attached chiral segments and enantiomers are as follows: being close to a chiral selector, one enantiomer with weaker interactions moves from the wider to the narrower edge of the CD along the exterior of the CD cavity, whereas the other with stronger interactions is always located at the wider edge of CD with only slight penetration into the cavity. This observation revealed that the differences in such an interaction mode is essential for effective enantioseparation.

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