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Theoretical Study of Enantiomer Recognition of β-Butyrolactone by Acetyl Cyclodextrins

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ABSTRACT

Cyclodextrins and their derivatives are widely used in chromatographic chiral seperation. Molecular mechanics was applied to study the enantiomer recognition of a chiral model, β-butyrolactone, by several acetyl derivatives of α-and β-cyclodextrins. At 0 K, β-butyrolactone bound near the wider rim of cyclodextrin rings. The stabilization energy of the complex formation, *in vacuo*, was in the range of -6 to -19 kcal/mol. It was found that *van der Waals* interaction was the major contribution for the host-guest complex formation. From this study, per(6-O-acetyl-2,3-di-O-methyl)-β-cyclodextrin (bcd-A) and per(6-O-dichloroacetyl-2,3-di-O-methyl)-β-cyclodextrin (bcd-2Cl) were found to be good chiral selectivity reagents with enantiomer differentiation energy of 4-5 kcal/mol.

Key words: cyclodextrins, enantiomer recognition, molecular mechanics

INTRODUCTION

Cyclodextrins (CDs) are cyclic oligosaccharides, consist of 6 to 12 D-glucose units which link together by α-1,4 glucosidic linkage. Such linkage forms a torus shape of CDs with primary hydroxyl groups at the narrower rim and secondary hydroxyl group at the wider rim. The cavity of CDs is less polar than other parts of molecule. The cavity size is determined by number of glucose units. α-, β-, and γ-CDs with glucose 6, 7, and 8 units, respectively, are the most available ones (Li and Purdy, 1992). CDs can form host-guest complexes with several classes of substances. As CDs possess a lot of chiral centers, they can discriminate stereoisomers including enantiomers. Recently, CDs have been widely used in chiral seperation as well as chromatography. Their popularity deduces from its readily available and inexpensive price. Moreover, CDs have possibility to coordinate with guests of differing sizes and functional groups due to the different cavity size and the easily derivatized ring system (Lipkowitz *et al*., 1997). Several classes of enantiomeric compounds i.e. sugars, alcohols, amines, lactones, epoxides, bicyclic compounds, were gas chromatographic resolved on derivatized CDs column (Armstrong *et al*., 1990; Schurig and Nowotny, 1990). This advance capability of cyclodextrin based chromatography has been widely applicable to pharmaceutical and food additive industries, fragrances and pheromone research (Lipkowitz *et al*., 1997; Armstrong *et al*., 1986). However, mechanism and important driving forces of the enantiomer recognition has not been clear yet. Nowadays, computational modeling has been a helpful tool to understand this topic (Armstrong *et al*., 1986; Schurig and Nowotny, 1990; Lipkowitz *et al*., 1998; Li *et al*., 1999; Dodziuk *et al*., 2000; Salvatierra *et al*., 2000). In

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this paper, the geometries of host-guest complexes between enantiomers of β-butyrolactone and acetyl derivatives of cyclodextrins are modeled.

MATERIALS AND METHODS

The starting geometries of α- and β-cyclodextrin were taken from the calculations of previous work (Parasuk *et al*., 1997). The acetyl derivatives of cyclodextrins were built by modification from α- and β-cyclodextrin. The geometries of enantiomers of β-butyrolactone, cyclodextrin derivatives, and their host-guest complexes were fully optimized using molecular mechanics with MM+ force field in Hyperchem package (Hypercube, 1996). The Polak-Ribiere conjugate gradient minimizer was used and the convergence condition was the gradient root mean square of below 0.001 kcal/mol/Å. Two orientations of β-butyrolactone in cyclodextrin complexes, i.e. methyl group pointing toward the primary and secondary hydroxyl rim, were considered. Since cyclodextrin has a lot of possible conformations, simulated annealing were carried out to find the lowest energy structure of each compound. The conditions of the simulated annealing are shown in Table 1.

The hosts studied in this work were acetyl derivatives of α- and β-cyclodextrin (acd and bcd). The derivatives were modified by substitution of hydrogen atom of the primary hydroxyl groups with acetyl (A), monochloroacetyl (1Cl), dichloroacetyl (2Cl), and trichloroacetyl (3Cl) groups. All the secondary hydroxyl groups of the cyclodextrin derivatives were substituted with methoxyl groups. The cyclodextrin derivatives used in this study and their abbreviation are given in Table 2.

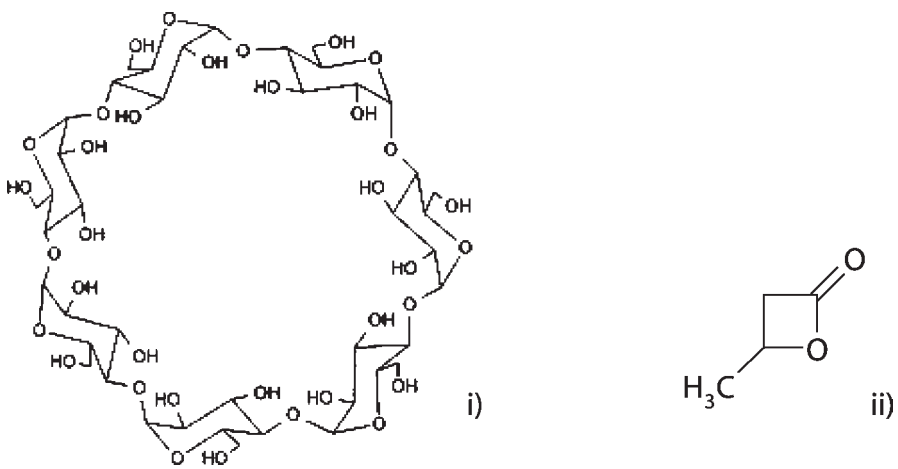


Figure 1 Molecular structures of i) β-cyclodextrin and ii) β-butyrolactone.

Table 1 Conditions of the simulated annealing.

Time (ps)		Temperature (K)	
Heat time	0.01	Starting temperature	0
Runtime	0.1	Simulation temperature	200
Cool time	3.0	Final temperature	0
Step time	0.001	Temperature step	20

Table 2 Cyclodextrins in this study.

Abbreviation	Cyclodextrins
acd-A	per(6-O-acetyl-2,3-di-O-methyl)-α-cyclodextrin
acd-1Cl	per(6-O-monochloroacetyl-2,3-di-O-methyl)-α-cyclodextrin
acd-2Cl	per(6-O-dichloroacetyl-2,3-di-O-methyl)-α-cyclodextrin
acd-3Cl	per(6-O-trichloroacetyl-2,3-di-O-methyl)-α-cyclodextrin
bcd-A	per(6-O-acetyl-2,3-di-O-methyl)-β-cyclodextrin
bcd-1Cl	per(6-O-monochloroacetyl-2,3-di-O-methyl)-β-cyclodextrin
bcd-2Cl	per(6-O-dichloroacetyl-2,3-di-O-methyl)-β-cyclodextrin
bcd-3Cl	per(6-O-trichloroacetyl-2,3-di-O-methyl)-β-cyclodextrin

RESULTS AND DISCUSSION

1. Structures of cyclodextrins and their host-guest complexes

The geometries of acd-A and bcd-A are shown in Figure 2. Because of the more flexible and larger cavity of cyclodextrin ring, the conical shape of bcd-A was more distorted than that of acd-A and one of the acetyl groups of bcd-A pointed toward its cavity. Similar structures were found for the other chloroacetyl derivative cyclodextrins. The acetyl substituents caused cyclodextrin ring deformation as Waraporn *et al*. (2001) reported that the conical shape of parent β-cyclodextrin and its methoxy derivative were quite symmetric.

The structures of the inclusion complexes of acd-A/R and bcd-A/R are displayed in Figure 3. In both complexes, as well as others which are not shown here, the β-butyrolactone bound, not inside the cavity, near the methoxyl groups at the wider rim of cyclodextrin cone. Upon the host-guest complex formation, the cyclodextrin rings of β-cyclodextrin derivatives were also more distorted than α-cyclodextrin derivatives.

2. Binding forces

Binding energies of the inclusion complexes, collected in Table 3, were the energy differences of the complexes and the summation of the corresponding hosts and guests. In Table 3, the heading E_{total} refers to the sum of the component force field MM+ energies. The heading E_{bond}, E_{angle}, $E_{dihedral}$, E_{vdw}, $E_{stretch\text{-}bend}$, and E_{elec} refer to the component energies of bond stretching, angle bending, dihedral angle torsion, *van der Waals* interaction, bending-stretching cross term, and electrostatic interaction, respectively. From Table 3, the binding energies of the complexes were in the range of –6 to –19 kcal/mol. The acd-3Cl formed the most stable complexes with both β-butyrolactone with stabilization energies of –16 and -19 kcal/mol, while the host-guest complexes of bcd-3Cl were the least stable ones. The major contribution of the binding energy was the energy caused by *van der Waals* force, ΔE_{vdw}. Among the chloroacetyl derivatives of β-cyclodextrin, the monochloroacetyl, bcd-1Cl, formed the most stable host-guest complexes while the trichloroacetyl, bcd-3Cl, formed the least stable ones. This is in good agreement with the chromatographic results reported by Shitangkoon and Vigh (1998).

3. Enantiomer recognition

The enantiomer recognition of cyclodextrin ($\Delta_r E$), exhibited in Table 4, was computed from the energy difference of their inclusion complexes with R- and S-β-butyrolactone,

$$\Delta_r E = E_R - E_S$$

where E_R and E_S are energies of corresponding R-

and S-β-butyrolactone cyclodextrin complexes. The bcd-A and bcd-2Cl showed the best enantiomer recognition with $\Delta_r E$ of –4 to -5 kcal/mol. The negative value expressed that the complex of R- was more stable than that of S- configuration. The important contribution to the enantiomer discrimination was the energy rising from dihedral angle torsion, $\Delta_r E_{dihedral}$, which was contributed from structural deformation.

CONCLUSION

The *van der Waals* interaction was the major contribution of the binding energy of the

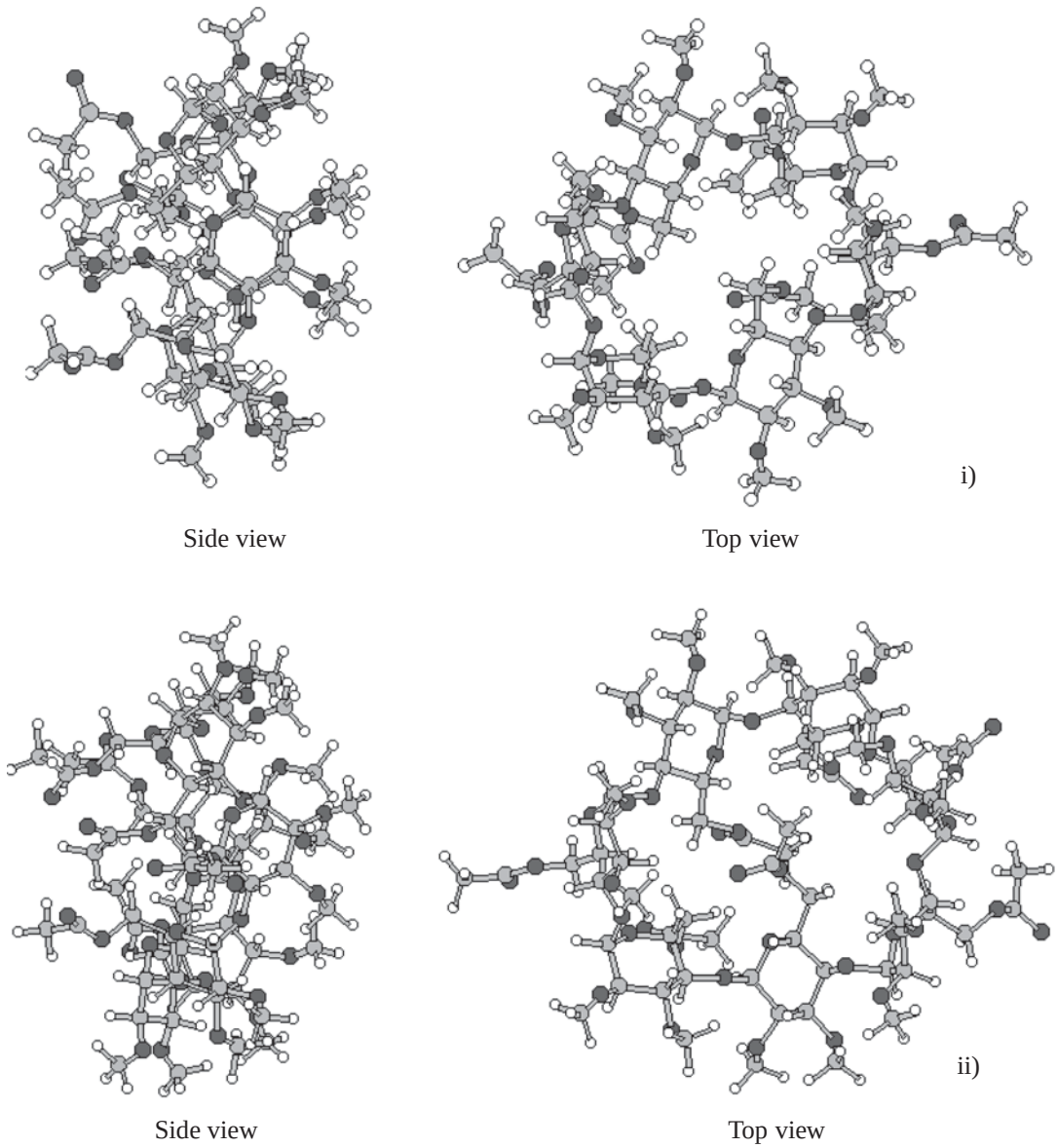
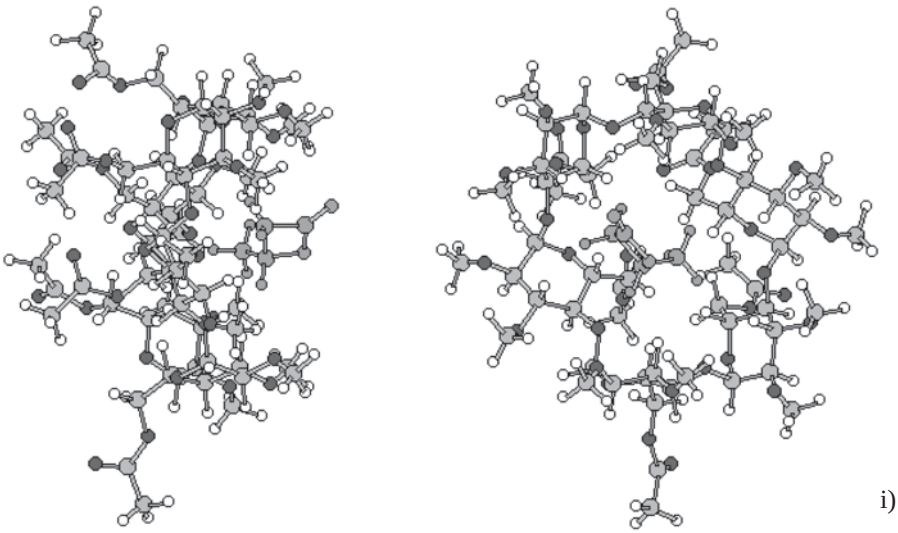


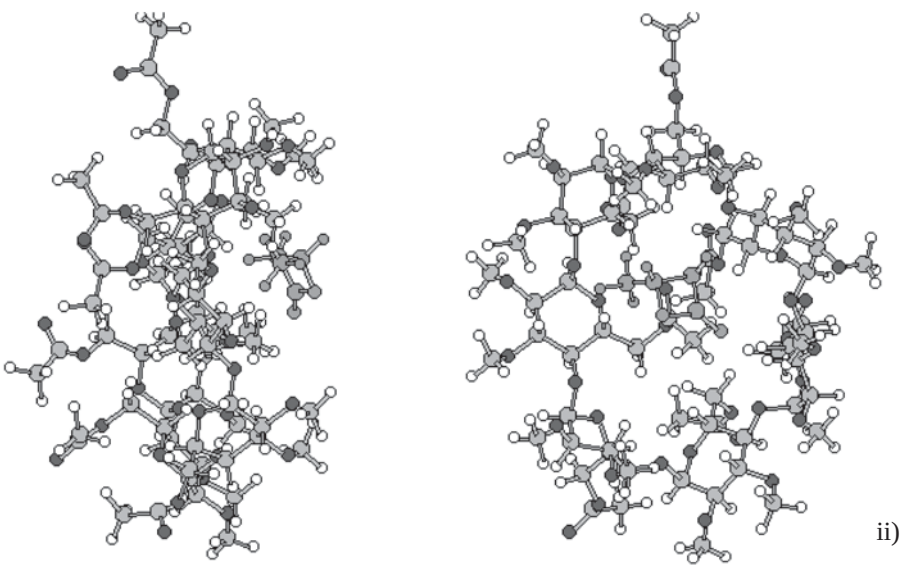
Figure 2 The side view (left) and top view (right) of optimized structures of host. i) acd-A and ii) bcd-A. (● = C, ● = O, ○ = H)

host-guest complex formation of cyclodextrins. The best enantiomer recognition host were per(6-O-acetyl-2,3-di-O-methyl)-β-cyclodextrin (bcd-A) and per(6-O-dichloroacetyl-2,3-di-O-methyl)-β-cyclodextrin (bcd-2Cl). The structural deformation of the cyclodextrin upon acetylation and complex formation was an important factor for the chiral selectivity.



i)

Side view Top view



ii)

Side view Top view

Figure 3 The side view (left) and top view (right) of optimized structures of host-guest complexes, i) acd-A/R and ii) bcd-A/R.
(● = C, ● = O, ○ = H, ● = β-butyrolactone)

Table 3 Binding energy (kcal/mol) of host-guest complexes.

	ΔE_{total}	ΔE_{bond}	ΔE_{angle}	$\Delta E_{dihedral}$	ΔE_{vdw}	$\Delta E_{stretch\text{-}bend}$	ΔE_{elect}
acd-A/R	-12.51	-0.11	-0.38	0.43	-11.35	0.02	-1.12
acd-A/S	-11.91	-0.15	0.12	-0.08	-10.77	-0.03	-1.00
acd-1Cl/R	-13.36	-0.09	-0.82	1.76	-13.42	0.03	-0.82
acd-1Cl/S	-12.37	-0.02	-0.72	1.59	-12.20	0.08	-1.10
acd-2Cl/R	-9.78	0.18	-0.58	0.85	-9.73	0.21	-0.71
acd-2Cl/S	-10.72	-0.05	0.31	0.39	-10.58	0.04	-0.82
acd-3Cl/R	-16.40	-0.17	-2.54	-0.92	-11.10	-0.07	-1.59
acd-3Cl/S	-18.75	-0.09	-3.03	-0.54	-13.43	-0.00	-1.65
bcd-A/R	-10.90	0.15	-3.07	-0.36	-7.09	0.15	-0.67
bcd-A/S	-6.49	0.26	-0.70	2.64	-8.68	0.33	-0.35
bcd-1Cl/R	-15.06	-0.12	0.88	-3.08	-11.17	-0.17	-1.38
bcd-1Cl/S	-14.42	0.18	6.69	-6.97	-13.47	0.09	-0.93
bcd-2Cl/R	-16.47	-0.18	4.72	-9.26	-10.76	-0.03	-0.96
bcd-2Cl/S	-11.05	-0.14	3.62	-1.71	-11.69	-0.06	-1.07
bcd-3Cl/R	-6.26	-0.09	-2.97	4.71	-7.91	-0.10	0.09
bcd-3Cl/S	-8.35	0.03	1.71	-0.27	-10.00	0.18	0.01

Table 4 Recognition energy (kcal/mol) of cyclodextrins.

	Δ_rE	Δ_rE_{bond}	Δ_rE_{angle}	$\Delta_rE_{dihedral}$	Δ_rE_{vdw}	$\Delta_rE_{stretch\text{-}bend}$	Δ_rE_{elect}
acd-A	-0.60	0.03	-0.49	0.50	-0.58	0.05	-0.12
acd-1Cl	-0.99	-0.08	-0.10	0.18	-1.22	-0.05	0.28
acd-2Cl	0.94	0.23	-0.90	0.46	0.85	0.17	0.11
acd-3Cl	2.35	-0.08	0.49	-0.38	2.32	-0.07	0.07
bcd-A	-4.42	-0.12	-2.37	-3.01	1.58	-0.17	-0.33
bcd-1Cl	-0.64	-0.31	-5.81	3.89	2.30	-0.26	-0.45
bcd-2Cl	-5.42	-0.04	1.10	-7.54	0.92	0.02	0.11
bcd-3Cl	2.09	-0.12	-4.68	4.98	2.10	-0.27	0.08

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