Ab initio Study of Chiral Recognition of β-Butyrolactone by Cyclodextrins

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Abstract. Separation of stereoisomers of organic compounds is an important and challenge task for chemists. Cyclodextrins and their derivatives have been widely used in chromatography for this application. Experimental results indicated that substituents on the hydroxyl groups of cyclodextrin affect the efficiency of the chiral separation of β-butyrolactone. The understanding of the interactions contributed to the chiral recognition of cyclodextrin would help us predict the separation capability of a specific pair of cyclodextrin and chiral compound. Thus, the cyclodextrin substituent effect on the chiral recognition should be systematically investigated. In this study, Hartree Fock method with 3-21G basis set and density functional theory B3LYP with 6-31G* basis set were applied to determine the chiral recognition of a chiral model, β-butyrolactone, by β-cyclodextrin and its derivatives. Both methods predicted comparable values of chiral recognition of β-cyclodextrin derivatives. We found that methoxyl substitution on the wider rim of cyclodextrin (secondary hydroxyl groups) give the most effective chiral separation (ΔΔE=18.2 kcal/mol in favor of R-isomer) followed by substitution on the narrow rim (ΔΔE=9.5 kcal/mol in favor of S-isomer) while substitution on both side give the worst recognition (ΔΔE=3.2 kcal/mol in favor of S-isomer). This suggests that β-cyclodextrin with substitution only on the wider rim give the best chiral selectivity. By replacing methyl group with chiral hydroxypropyl group, we found that the chiral selectivity is reduced (ΔΔE=6.4 and 8.4 kcal/mol respectively for R- and S-form of hydroxypropyl group). This implies that the bulky group causes the reduction of the chiral selectivity.

1 Introduction

Cyclodextrins (CDs) are cyclic α-1,4 linked oligosaccharides of D-glucose units. The most naturally available are α-, β-, and γ-CDs with 6, 7, and 8 glucose units. Such a linkage forms a truncated cone shape of CDs with the 6-primary hydroxyl groups of glucose at the narrower and the 2- and 3- secondary hydroxyl groups at the wider rim. The cavity of CDs is less polar than other parts of molecule.[1] The cavity size varies from 5 to 9 Å depending on numbers of glucose units. CDs can form inclusion

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complexes with several classes of substances. Several factors govern the stability of the complexes. Since CDs have a lot of chiral centers, they can form diastereomers with enantiomeric guests with different stability. Thus, CDs are utilized as reagents for chiral separation. One of such applications is the usage of CDs as either stationary or mobile phase in chromatographic separation of isomers.[2] Several classes of enantiomeric compounds i.e. sugars, alcohols, amines, lactones, epoxides, bicyclic compounds, were gas chromatographic resolved on derivatized CDs column.[3,4] This capability of cyclodextrin in chromatography has been widely applied to pharmaceutical and food additive industries, fragrances, and pheromone res- earch.[2,5] Shitangkoon and Vigh reported that trichloroacetyl substituents on β-cyclodextrin, as stationary phase in gas chromatography, gives good column efficiency while monochloroacetyl yields good selectivity of the chiral separation of β-butyrolactone.[6] They found furthermore that dichloroacetyl substitution gives the compromised results of the column efficiency and the chiral selectivity. Substituents seem to have an effect on the chiral separation of the chromatographic column. To understand the substitution effect on the chiral separation by cyclodextrin, the inclusion phenomenon between β-cyclodextrins and β-butyrolactone were investigated using computational modeling techniques.

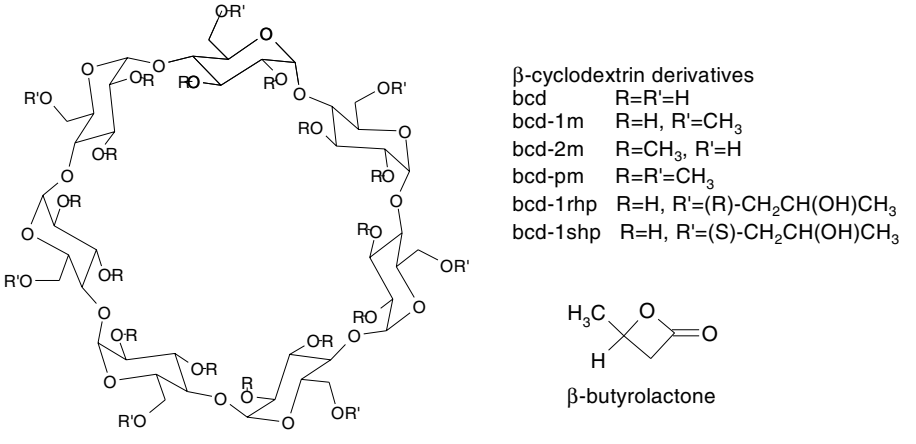

Fig. 1. Structure of β-cyclodextrin derivatives and β-butyrolactone

2 Computational Details

Illustrative representation of β-cyclodextrin derivatives and β-butyrolactone are displayed in Figure 1. Cyclodextrins studied in this work were β-cyclodextrin, denoted as bcd, and its derivatives. The derivatives were modified by substitution of hydroxyl with methoxyl groups. The suffixes 1m, 2m, or pm expressed for methoxyl substituted at primary, secondary, or both rims of the parent cyclodextrin, i.e. bcd-1m, bcd-2m, and bcd-pm stand for per(6-O-methyl)-β-cyclodextrin, per(2,3-di-O-methyl)-β-cyclodextrin, and per(2,3,6-tri-O-methyl)-β-cyclodextrin, respectively. Moreover, the substitution of

the primary hydroxyl with chiral substituents, R- and S-2-hydroxypropoxyl, i.e. per(6-O-R-2-hydroxymethyl)-β-cyclodextrin and per(6-O-S-2-hydroxymethyl)-β-cyclodextrin denoted as bcd-1rhp and bcd-1shp, were also studied. Geometries of host β-cyclodextrin and derivatives, together with those of enantiomers of guest β-butyrolactone, and their host-guest complexes were taken from our previous work where molecular dynamics simulations of the inclusion complexes between bcd and β-butyrolactone were performed.[7] In that study, two orientations of β-butyrolactone i.e. one with methyl group pointing inward and another with methyl group pointing outward the secondary end of the cyclodextrin, were considered. In this work, energies of the more stable complexes, hosts, and guests were recalculated at Hartree Fock level with 3-21g basis set and density functional theory level using B3LYP functionals with 6-31g* basis set. The *ab initio* and DFT calculations were performed using Gaussian98 program [8].

3 Results and Discussion

3.1 Binding Energies

Binding energies, ΔE, of the inclusion complexes were computed from the energy differences between complexes and corresponding host and guest molecules.

$$\Delta E_{R/S} = E_{R/Scpx} - (E_{host} + E_{R/S})$$

$E_{R/Scpx}$ is the energy of R- or S-β-butyrolactone and cyclodextrin complex. E_{host} is the energy of free cyclodextrin derivative, and $E_{R/S}$ is the energy of guest R- or S-β-butyrolactone. Table 1 displays binding energies of inclusion complexes between bcd derivatives and R- and S-β-butyrolactone. From the table, HF and B3LYP gave similar trend of binding energies, even though HF seems to overestimate the binding energies as compared to the results obtained at B3LYP level. For instances, HF predicted both bcd and bcd-2m bind to S-β-butyrolactone with the binding energy of -5.3 and -2.7 kcal/mol, respectively, while B3LYP predicted that S-β-butyrolactone does not bind with bcd and bcd-2m (ΔE_S = 0.4 and 4.6 kcal/mol). The deficiency of HF/3-21g in the study of cyclodextrin complex where weak interaction is involved is clearly seen. Considering the inclusion behavior of R-β-butyrolactone, it is observed that the R-enantiomer could not bind with bcd and bcd-1m, as indicated by

Table 1. Binding energies (ΔE_R and ΔE_S, kcal/mol) of the complexes between R- and S-β-butyrolactone and β-cyclodextrin and derivatives calculated by HF/3-21g and B3LYP/6-31g*

	HF/3-21g		B3LYP/6-31g*	
	ΔE_R	ΔE_S	ΔE_R	ΔE_S
Bcd	1.9	-5.3	6.2	0.4
bcd-1m	0.5	-11.1	1.9	-7.7
bcd-2m	-22.1	-2.7	-13.6	4.6
bcd-pm	-19.4	-24.8	-14.3	-17.4

the positive ΔE_R while it forms complexes with bcd-2m and bcd-pm (ΔE_R = -13.6 and -14.3 kcal/mol, respectively). On the other hand, the S-β-butyrolactone forms complexes with bcd-1m and bcd-pm (ΔE_S = -7.7 and -17.4 kcal/mol, respectively) while it does not bind with bcd and bcd-2m. It could be seen that the complexation pattern with bcd and bcd derivatives of the R- and S- enantiomers of β-butyrolactone is distinctive. Thus, the degree of methylation of β-cyclodextrin affected the stability of the inclusion complex of β-butyrolactone differently for the different enantiomers.

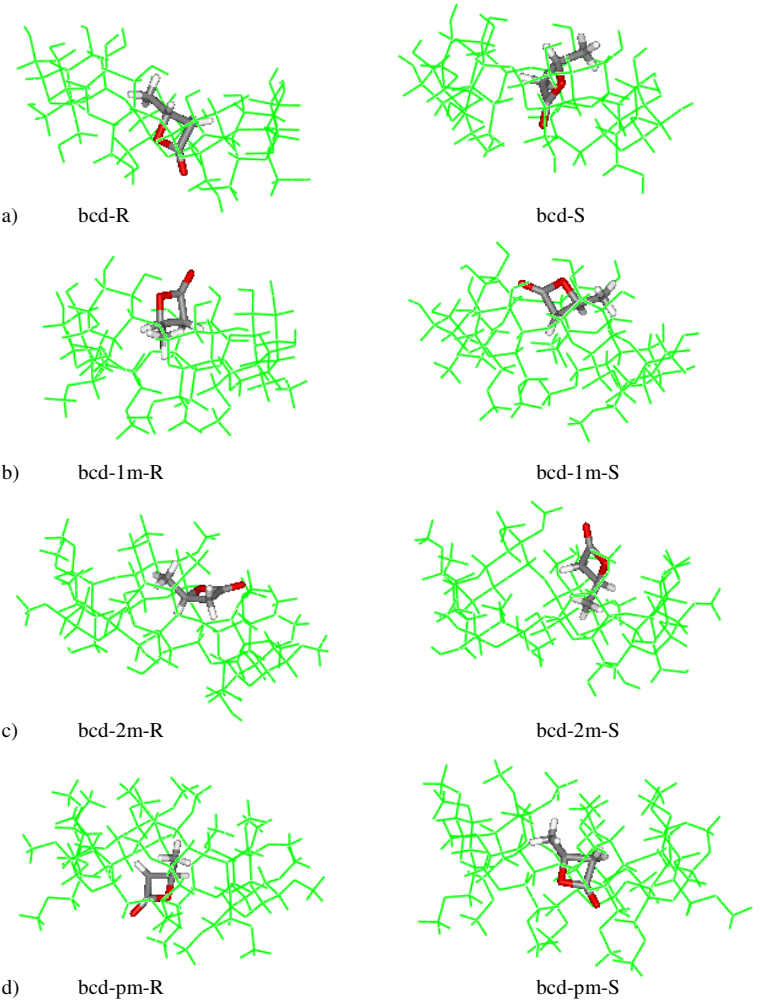

Fig. 2. Side view of inclusion complexes of R- and S-β-butyrolactone with derivatives of β-cyclodextrin, a) bcd, b) bcd-1m, c) bcd-2m, and d) bcd-pm. The cyclcodextrin skeletons are presented as thin line, β-butyrolactone are presented as color stick with ● ● ○ for C, O, and H, respectively. In all figure the upper side is the wider secondary rim[7].

Figure 2 shows structures of inclusion complexes of bcd and its derivatives with R- and S-β-butyrolactone obtained from MD simulation.[7] In the complex between bcd and R- and S-β-butyrolactone, the guests were placed inside the cavity of bcd as shown in Figure 2a. However, these are not the stable complexes since their binding energies are positive. From Figure 2b, the methyl group of the guest S-β-butyrolactone pointed outward to the wider secondary hydroxyl groups of the bcd-1m, while the methyl group of R-enantiomer pointed inward to the ring. The former forms the more stable complex than the latter. This evidence was also observed in the complexes of host bcd-2m. In figure 2c, the R-enantiomer forms the more stable complex (ΔE_R = -13.6 kcal/mol) and its methyl group points outward to the wider end of the cyclodextrin ring. The S-enantiomer which forms less stable complex, however, has its methyl group points inward to the cyclodextrin ring. The host bcd-pm, in which the hydroxyl groups on both ends are methylated, forms complexes with both enantiomers with comparable stability. As displayed in figured 2d, the orientation of the R- and S-guests in both complexes are similar, the guest situated inside the cavity and the methyl group of the guest points outward to the secondary end. It is interesting to note that stable complexes of bcd-1m (with S-enantiomer) and bcd-2m (with R-enantiomer) have the methyl group point outwad the bcd ring while the unstable ones have the methyl group points inward. This is also the case for bcd-pm where both R- and S-enantiomers have the methyl group point outward the secondary methoxyl rim. The orientation of the guest is very important for the formation of the stable complex.

3.2 Chiral Recognitions

The chiral recognition of cyclodextrin ($\Delta\Delta E$), exhibited in Table 2, was computed from the difference of the binding energies of both enantiomers, ΔE_R and ΔE_S, or from the energy difference of their inclusion complex with R- and S-β-butyrolactone,

$$\Delta\Delta E = \Delta E_R - \Delta E_S \qquad \text{or} \qquad \Delta\Delta E = E_{Rcpx} - E_{Scpx}$$

where E_{Rcpx} and E_{Scpx} are energies of corresponding R- and S-β-butyrolactone cyclodextrin complexes. Larger $\Delta\Delta E$ means more efficient chiral separation. The bcd-2m showed the best chiral recognition with $\Delta\Delta E$ of -19 and -18 kcal/mol by HF and B3LYP methods, respectively. Though the different level of accuracy predicts different values of binding energy of the complexes, there is not much different in the chiral recognition prediction. The negative value expressed larger binding energy for R- than for S- configuration and vice versa for the positive value. Having the smaller $\Delta\Delta E$ (in magnitude), bcd-1m has a moderate value of $\Delta\Delta E$ and also could be used for chiral separation. Though a moderate value was obtained, bcd might not be suitable to use as chiral selective reagent as it gave positive value of the binding energy to both enantiomers of β-butyrolactone. Thus, the methylation of the secondary as well as the primary hydroxyl groups of cyclodextrin could improve its chiral selectivity. The methylation of the secondary hydroxyl improves the binding with R-enantiomer

whereas the methylation of the primary hydroxyl improves the binding with S-enantiomer. There are not much difference on the ΔΔE of bcd-1m, bcd-1rhp, and bcd-1shp (all have the substituents on the primary hydroxyl groups), i.e. 9.5, 6.4, and 8.4 kcal/mol, respectively. Positive values of ΔΔE confirmed that the substituents on the primary rim improve the stability of the complex of the S-enantiomer. Thus, the chiral R- or S-2-hydroxypropyl did not change the chiral preference of cyclodextrin. When the hydroxyl groups on both rims of bcd are methylated as in bcd-pm, R- and S-β-butyrolactone bind to the host favorably. They form complex with the host with comparable stability and hence leads to small ΔΔE, not suitable to use as chiral selective reagent. Thus, the host which forms the more stable complex (greater binding energy) is the more chiral selective (in exception of bcd-pm in which it forms stable complex with both R- and S-forms). A similar conclusion could also be observed from the gas chromatographic experiment.[6] In that study, the monochloroacetyl derived bcd gives the best chiral selectivity as compared to the dichloro- and the trichloroacetyl substituted bcds since it forms the most stable complex as implying from its largest retention time.

Table 2. Chiral recognition energies (ΔΔE, kcal/mol) of β-cyclodextrin and derivatives calculated by HF/3-21g and B3LYP/6-31g*

	ΔΔE	
	HF/3-21g	B3LYP/6-31g*
bcd	7.1	5.8
bcd-1m	11.5	9.5
bcd-2m	-19.5	-18.2
bcd-pm	5.4	3.2
bcd-2rhp	9.5	6.4
bcd-2shp	13.4	8.4

4 Conclusions

The stability of the inclusion complexes of β-cyclodextrin derivatives with β-butyrolactone depends on the degree of methylation of β-cyclodextrin. The derivative bcd-pm, where all the hydroxyl groups are methylated, forms stable complexes with both configurations of β-butyrolactone and is not very good in the chiral recognition. From this study, bcd-2m exhibited the best capability of the chiral recognition for β-butyrolactone and is recommended to use as the chiral selective agent. The bcd, on the other hand, has positive binding energies for both R- and S-β-butyrolactone is expected to give poor chiral recognition. Though HF method seems to overestimate the binding energies of the inclusion complexes, both HF and B3LYP methods predicted comparable values of chiral recognitions of β-cyclodextrin derivatives.

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References

1. Li, S., Purdy, W.C.: Cyclodextrins and Their Applications in Analytical Chemistry. Chem. Rev. 92 (1992) 1457-1470
2. Lipkowitz, K. B., Pearl, G., Coner, B., Peterson, M. A.: Explanation of Where and How Enantioselective Binding Takes Place on Permethylated β-Cyclodextrin, a Chiral Stationary Phase used in Gas Chromatography. J. Am. Chem. Soc. 119 (1997) 600-610
3. Armstrong, D.W., Li, W., Chang, C.-D., Pitha, J.: Polar-liquid, Derivatized Cyclodextrin Stationary Phases for the Capillary Gas Chromatography Separation of Enantiomers. Anal. Chem. 62 (1990) 914-923
4. Schurig, V., Nowotny, H.-P.: Gas Chromatographic Separation of Enantiomers on Cyclodextrin Derivatives. Angew. Chem. Int. Ed. Engl. 29 (1990) 939-957
5. Armstrong, D. W., Ward, T.J., Armstrong, R. D., Beesley, T. E.: Separation of Drug Stereoisomers by the Formation of β-Cyclodextrin Inclusion Complexes. Science 232 (1986) 1132-1135
6. Shitangkoon, A., Vigh, G.: Gas Chromatographic Enantiomer Separations using Chloroacylpentyl Cyclodextrins. Abstracts of the 24th Congress on Science and Technology of Thailand, Bangkok (1998) 218-219
7. Parasuk, W., Longwan, N., Tasanakosol W.: Enantiomer Recognition of of β-Butyrolactone by Cyclodextrin. The fifth Annual National Symposium on Computational Science and Engineering, Bangkok (2001) 187-193
8. Gaussian 98, Revision A9, Frisch, M. J., Trucks, G. W., Schlegel, H. B., Scuseria, G. E., Robb, M. A., Cheeseman, J. R., Zakrzewski, V. G., Montgomery, Jr., J. A., Stratmann, R. E., Burant, J. C., Dapprich, S., Millam, J. M., Daniels, A. D., Kudin, K. N., Strain, M. C., Farkas, O., Tomasi, J., Barone, V., Cossi, M., Cammi, R., Mennucci, B., Pomelli, C., Adamo, C., Clifford, S., Ochterski, J., Petersson, G. A., Ayala, P. Y., Cui, Q., Morokuma, K., Malick, D. K., Rabuck, A. D., Raghavachari, K., Foresman, J. B., Cioslowski, J., Ortiz, J. V., Baboul, A. G., Stefanov, B. B., Liu, G., Liashenko, A., Piskorz, P., Komaromi, I., Gomperts, R., Martin, R. L., Fox, D. J., Keith, T., Al-Laham, M. A., Peng, C. Y., Nanayakkara, A., Challacombe, M., Gill, P. M. W., Johnson, B., Chen, W., Wong, M. W., Andres, J. L., Gonzalez, C., Head-Gordon, M., Replogle, E. S., and Pople, J. A., Gaussian, Inc., Pittsburgh PA (1998)