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Short communication

# Thermodynamic study on the gas chromatographic separation of the enantiomers of aromatic alcohols using heptakis(2,3-di-*O*-methyl-6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin as a stationary phase

Aroonsiri Shitangkoon[a,*], Jirawit Yanchinda[a], Juwadee Shiowatana[b]

[a] *Department of Chemistry, Faculty of Science, Chulalongkorn University, Bangkok 10330, Thailand*
[b] *Department of Chemistry, Faculty of Science, Mahidol University, Bangkok 10400, Thailand*

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**Abstract**

Gas chromatographic separation of the enantiomers of nineteen structurally related aromatic alcohols was investigated as a function of temperature using a heptakis(2,3-di-*O*-methyl-6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin-coated capillary column. Thermodynamic parameters were determined and compared with those obtained with the nonchiral, reference stationary phase, OV-1701. While the $-\Delta H$ and $-\Delta S$ values for the more retained enantiomers of all nineteen alcohols are comparable on the chiral stationary phase used, the $-\Delta(\Delta H)$ and $-\Delta(\Delta S)$ values are considerably different. Of all the solutes tested, enantiodiscrimination was the greatest for the 2,6-difluoro-α-methylbenzyl alcohol.


*Keywords:* Cyclodextrin; Enantiomer; Thermodynamic parameters; Aromatic alcohols

## 1. Introduction

Due to their chirality and ability to form inclusion complexes with several types of compounds, cyclodextrins (CDs) and their derivatives are among the most commonly used chiral selectors in chromatography and electrophoresis [1–2]. A large number of CD derivatives [3–4], including the alkyl and acyl derivatives of (6-*O*-*tert*-butyldimethylsilyl)-CDs [5–9] have been prepared and were found to be versatile chiral selectors in GC. However, the interactions between various analytes and the modified CDs that lead to enantiomer separations are not yet understood in sufficient detail. Consequently, stationary phases are still selected by trial-and-error. Therefore, systematic studies on the relationship between the extent of enantioresolution and the structure of the analytes and the derivatized CDs are still needed to gain a better understanding of the separation process.

In this work, the enantiomers of nineteen 1-phenylethanol derivatives were eluted at different temperatures off of two GC capillary columns: one coated with an OV-1701 reference phase and another coated with heptakis(2,3-di-*O*-methyl-6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin (MeTBDMSβCD) in OV-1701. The retention factors, enantioselectivities and thermodynamic parameters for the separation of the enantiomers were determined to study the relationship between the structure of analyte and the extent of enantiorecognition afforded by MeTBDMSβCD.

## 2. Experimental

Separations were obtained on an Agilent 6890 gas chromatograph (Agilent Technologies, Wilmington, DE, USA), equipped with a split/splitless injector and a flame ionization detector. The injector and detector were maintained at 250 °C. Hydrogen was used as the carrier gas at an average linear velocity of 50 cm/s. Two deactivated 30 m ×

* Corresponding author. Tel.: +66 2 218 7608; fax: +66 2 254 1309.
*E-mail address:* aroonsiri.s@chula.ac.th (A. Shitangkoon).

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0.25 mm i.d. fused-silica capillary columns (Agilent) were statically coated with the dichloromethane solutions of the stationary phases, OV-1701 (Supelco, Bellefonte, PA, USA) and 25% MeTBDMSβCD in OV-1701, to obtain an identical film thickness of 0.25 μm. MeTBDMSβCD was prepared using the procedure of Takeo et al. [10] and was purified as described in [11]. Both columns were characterized by the Grob test [12,13]. Column efficiency was determined at 80 and 160 °C with *n*-alkanes and proved to be in the 3700–4200 plates/m range ($k' > 4$). All separations were performed isothermally, in duplicate, at 10 °C intervals in the temperature range of 80–190 °C. Most analytes were purchased from Aldrich (Milwaukee, WI, USA) and Fluka (Buchs, Switzerland), and used as received. Some compounds were prepared by reduction of the corresponding acetophenones and their structures were confirmed by $^1$H NMR. The structures of all analytes used in this study are shown in Fig. 1.

## 3. Results and discussion

Thermodynamic parameters ($-\Delta H$ and $-\Delta S$ values) associated with the interactions between the alcohol analytes and the gas chromatographic stationary phases were obtained from the relationship between the retention factor ($k'$) and the separation temperature according to:

$$\ln k' = -\frac{\Delta H}{RT} + \frac{\Delta S}{R} - \ln \beta \quad (1)$$

where $R$ is the universal gas constant and $\beta$ is the ratio of the mobile phase volume and the stationary phase volume. All $\ln k'$ versus $1/T$ plots were linear with $R^2$ values greater than 0.998.

The $-\Delta H$ values obtained for the two stationary phases are compared in Fig. 2a. All analytes had similar $-\Delta H$ values on the OV-1701 reference stationary phase indicating that they all interacted with the stationary phase in an essentially similar manner. On the chiral stationary phase, higher $-\Delta H$ values were observed for the more retained enantiomer of every analyte indicating that they interacted with the modified cyclodextrin more strongly than with OV-1701. Nevertheless, the $-\Delta H$ values were still comparable among all the analytes on the MeTBDMSβCD phase. Similar trend was also observed for $-\Delta S$ values.

The enantiomers of all nineteen alcohols included in this study could be resolved with the MeTBDMSβCD-coated column. The corresponding $-\Delta(\Delta H)$ and $-\Delta(\Delta S)$ values were determined from the $\ln \alpha$ versus $1/T$ plots according to:

$$\ln \alpha = -\frac{\Delta(\Delta H)}{RT} + \frac{\Delta(\Delta S)}{R} \quad (2)$$

and $-\Delta(\Delta H)$ values are shown in Fig. 2b. Similar trend was also obtained for $-\Delta(\Delta S)$ values. All $\ln \alpha$ versus $1/T$ plots were linear except for solutes **14** and **16** (Fig. 3) that, despite strictly linear $\ln k'$ versus $1/T$ plots, displayed separation selectivity maxima. Considering that only analytes **14** and **16** had a polar functional group (–$COOCH_3$) and an electron-attracting group (–$CF_3$) adjacent to the –CH(OH)– stereogenic center, respectively, it is likely that analytes **14** and **16** interacted with the stationary phase by multiple mechanisms [14] and no single mechanism dominated.

Although the enantiomers of all alcohol analytes could be separated with the MeTBDMSβCD-coated column, the degree of enantioseparation differed significantly (Fig. 2b). Using alcohol **1** as a reference compound, substitution of the methyl group at the stereogenic center with longer (**3**, **4**) or bulkier (**13**) alkyl groups or an electronegative ester group

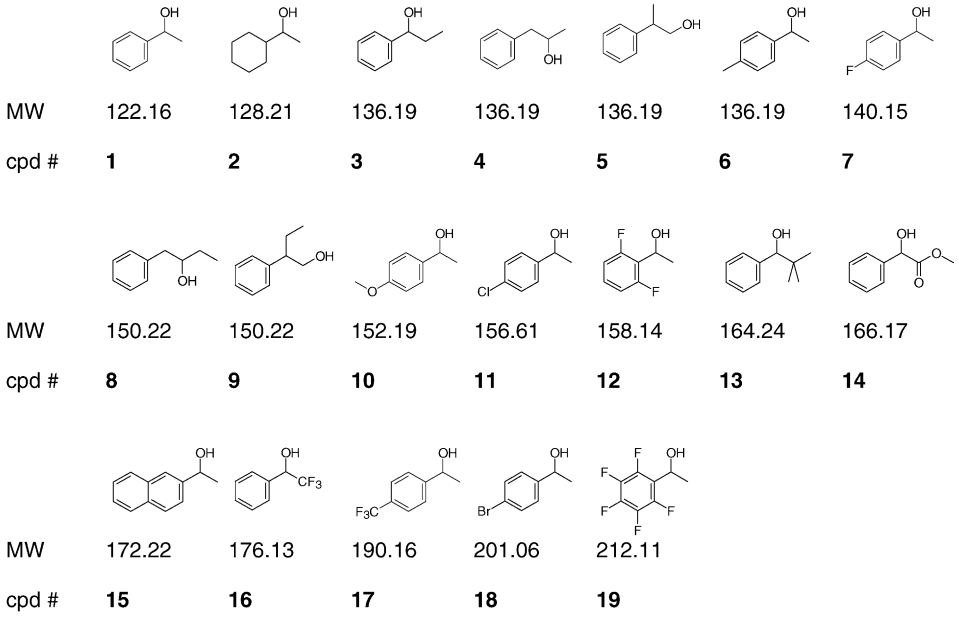


Fig. 1. Structure and molecular weight of the analytes tested.

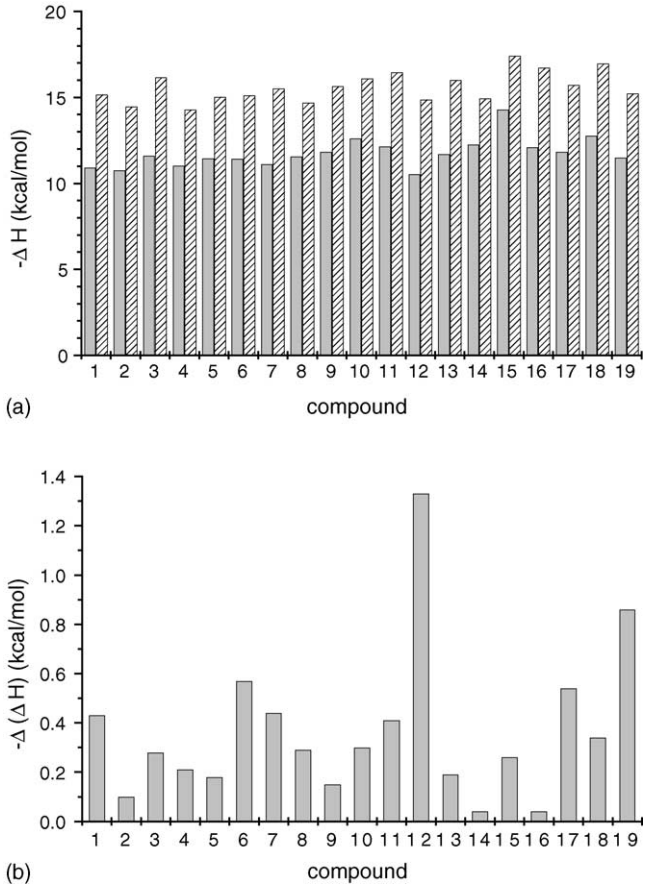


Fig. 2. (a) $-\Delta H$ values for the nineteen alcohols tested on the OV-1701-coated column (solid bars) and for the more retained enantiomers tested on the MeTBDMSβCD-coated column (hatched bars); (b) $-\Delta(\Delta H)$ values for the enantiomeric pairs of the nineteen alcohols separated on the MeTBDMSβCD-coated column.

(**14**) or trifluoromethyl group (**16**) reduced the separation selectivity significantly. On the contrary, replacement of the methyl group at the *para*-position of the aromatic ring with a trifluoromethyl group (analytes **6** versus **17**) had no effect on the separation and the respective $-\Delta(\Delta H)$ and $-\Delta(\Delta S)$ values were practically indistinguishable. A comparison of the $\ln\alpha$ versus $1/T$ plots of alcohols **1** and **16** indicates that temperature had a strong influence on the separation of the enantiomers of **1** but only a minor effect on the separation of the enantiomers of **16**. At temperatures above 150 °C, separation selectivity for the enantiomers of **16** is better than for **1**, but below 150 °C the opposite is true (Fig. 3).

The effect of electronegative substituents on the separation of enantiomers is further demonstrated by Fig. 4a–c: replacement of all hydrogen atoms on the aromatic ring with fluorine atoms improved the separation of the enantiomers (Fig. 4b). The number and position of electronegative substituents is very important: 2,6-difluoro-α-methylbenzyl alcohol (**12**) exhibited the greatest $-\Delta(\Delta H)$ and $-\Delta(\Delta S)$ values and best separation (Fig. 4c) among the analytes tested.

Comparison of the results obtained for the *para*-substituted alcohols (**6**, **7**, **10**, **11**, **17**, and **18**) revealed that

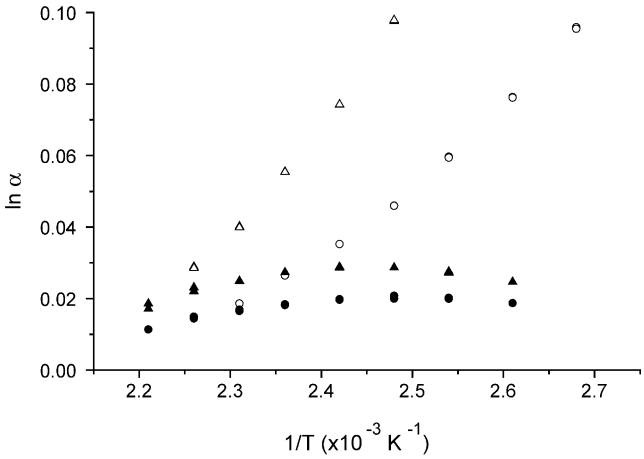


Fig. 3. $\ln\alpha$ vs. $1/T$ plots for the enantiomers of alcohols **1** (◯), **14** (●), **16** (▲), and **19** (△) on the MeTBDMSβCD-coated column.

both $-\Delta(\Delta H)$ and $-\Delta(\Delta S)$ decreased in the order of **6** > **17** > **7** > **11** > **18** > **10** (methyl > trifluoromethyl > fluoro > chloro > bromo > methoxy) and differences between the fluoro-, chloro-, and bromo-substituted derivatives were minor.

Comparison of the separation of the enantiomers of analytes **1**, **2**, and **15** indicated that separation selectivity on the MeTBDMSβCD-coated column was higher for the enantiomers of the alcohols that had an aromatic group (such as

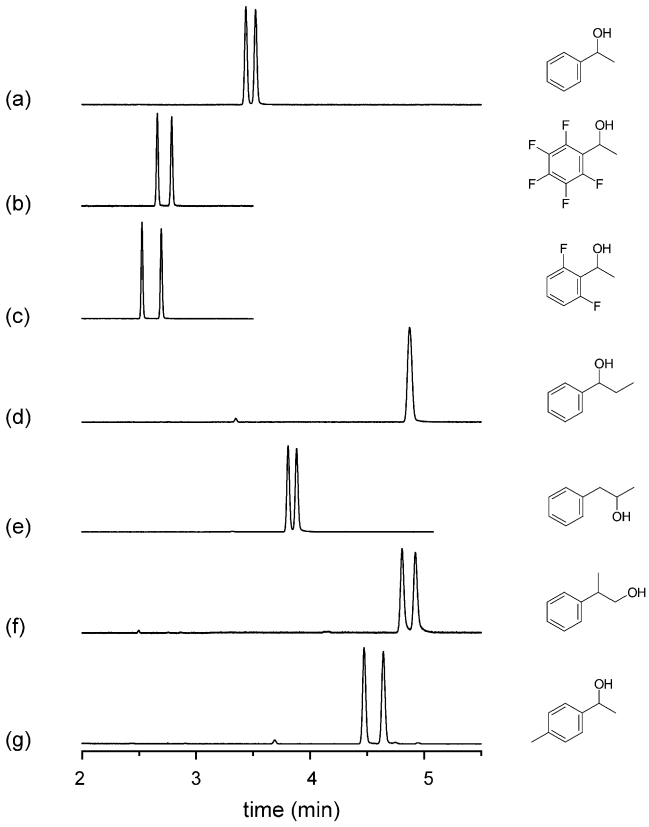


Fig. 4. Isothermal separation of the enantiomers of alcohols **1** (a), **19** (b), **12** (c), **3** (d), **4** (e), **5** (f), and **6** (g) on the MeTBDMSβCD-coated column at 140 °C.

**1** and **15**) than for the alcohols that had a cyclic aliphatic group (such as **2**). For the analytes that are isomers (**3**–**6** and **8**–**9**), changes in substituent position can also create a substantial change in separation selectivity. As shown in Fig. 4d–g, the enantiomers of all analytes could be separated at 140 °C except those of analyte **3**. Although, the $-\Delta(\Delta H)$ and $-\Delta(\Delta S)$ values are higher for analyte **3** than for analytes **4** and **5**, the enantiomers of analyte **3** could only be separated at lower temperatures requiring, unavoidably, more analysis time. Therefore, several aspects must be considered simultaneously in selecting the optimum separation conditions.

## 4. Conclusion

Investigation of the separation of the enantiomers of 1-phenylethanol derivatives as a function of temperature using MeTBDMSβCD as chiral selector indicates that the $-\Delta H$ and $-\Delta S$ values of all alcohols studied are quite similar to each other on the polysiloxane stationary phase, and the cyclodextrin-containing stationary phase. Nonetheless, there are several variables related to the structure of the analytes, e.g. size, polarity and position of the substituent, which influence the extent of enantiorecognition. Often, a slight change in analyte structure lead to a large difference in the separation selectivity. For the analytes studied, substitution on the aromatic ring of the alcohol tends to promote enantiodifferentiation, whereas substitution on the side chain is likely to reduce enantiodifferentiation. Systematic studies with larger sets of structurally related analytes will be needed to gain detailed insight into the separation mechanisms of cyclodextrins and, ultimately, be able to a priori predict the expected degree of separation for the enantiomers of an analyte based on its structure.

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