



# Measurements of association constants between enantiomers and chiral selectors by capillary gas chromatography. Theoretical and practical considerations

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## ARTICLE INFO

### Article history:

Received 19 September 2013

Received in revised form 4 November 2013

Accepted 5 November 2013

Available online 20 November 2013

### Keywords:

Chiral gas–liquid chromatography

Association constants

Capillary columns

Octakis(3-O-butanoyl-2,6-di-O-pentyl)- $\gamma$ -cyclodextrin

## ABSTRACT

The association constants of several volatile enantiomers with octakis(3-O-butanoyl-2,6-di-O-pentyl)- $\gamma$ -cyclodextrin at temperatures between 50 and 100 °C were measured by gas–liquid chromatography using capillary columns coated with different amounts of chiral selector dissolved in polysiloxane OV-1701 and prepared with a precisely determined phase ratio. Simple expressions were deduced to estimate the apparent distribution constants from accurate hold-up and retention times along with that known phase ratio at each temperature. The enantiomer–chiral selector association constants were then calculated from the linear regression of the apparent constants as a function of the chiral selector concentration. One aim of this study consisted in discussing all the experimental uncertainties inherent in the determination of enantiomer/selector association constants with chiral analytes, and how these fundamental measurements can be performed precisely without resorting to the use of reference solutes.

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## 1. Introduction

Derivatives of cyclodextrins (CDs) are widely used as stationary phases for enantioseparations of volatile compounds in chiral gas chromatography (GC) [1,2]. These cyclic molecules have five stereogenic centers in every glucose moiety. This large number of stereogenic centers in addition to the conical structure of the CD molecule which can induce solute inclusion into the cavity explains their broad chiral recognition capability. Octakis(3-O-butanoyl-2,6-di-O-pentyl)- $\gamma$ -cyclodextrin is composed of eight glucose units whose hydroxyl groups were converted in either ether or ester groups. This chiral selector (CS) is well soluble in polysiloxanes of medium polarities, and the columns based on this CD display chiral enantioselectivity toward a very broad group of chiral molecules [3,4].

GC using packed columns constitutes a well-accepted method for determining gas–liquid partitioning as well as complexation constants between a given selector and specific volatile compounds. This approach is highly precise provided that adsorption onto the support is negligible. The technique has been extensively used also in chiral chromatography [5]. Since, however, most CSs usually exhibit selectivity factors rarely exceeding

1.3 units, capillary columns containing the CS in question constitute a potentially better alternative. The use of capillary columns results in enough efficiency to compensate for the usually only moderate enantioselectivity of CSs. Moreover, the absence of a solid support makes the system much simpler and more accurate for the measurement of any gas–liquid equilibrium property [6].

Capillary columns have been widely used to estimate association constants by resorting to the retention increment model [7,8]. In that approach, a reference solute, usually an *n*-alkane is chromatographed along with the chiral solute. This reference molecule is chosen so as to have no interactions with the CS, and this very practical approach allows a distinction between retention contributions from both the nonchiral and the chiral components of the stationary phase and circumvents the necessity for knowledge of the phase ratio of the different columns.

The aim of this work was: (i) to discuss the direct measurement of association constants between a chiral selector and an enantiomer using capillary columns of exactly measured phase ratios; (ii) to apply simple fundamental equations to obtain the association constants of several enantiomers with the CS octakis(3-O-butanoyl-2,6-di-O-pentyl)- $\gamma$ -cyclodextrin dissolved in OV1701; (iii) to critically evaluate the uncertainties associated to each experimental measurement and how these uncertainties would affect the association constants; (iv) to evaluate the contribution of the achiral matrix to the apparent enantioselectivity factors, and (v) to critically compare the constants obtained here with the values that

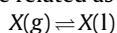
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would be estimated from the retention increment model under the same conditions.

## 2. Theoretical

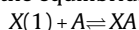
When an enantiomer  $X$  is chromatographed in a column containing a pure solvent  $S$  (e.g. polysiloxane), the solute infinite dilution gas–liquid partition coefficient,  $K_L^\circ$ , and retention factor are related as follows: [9]



$$K_L^\circ = k^\circ \beta^\circ = \frac{RT}{\gamma_S^\infty p^\circ v_s} \quad (1)$$

where  $k^\circ$  denotes the solute retention factor in a column having a phase ratio  $\beta^\circ$  (i.e. the ratio between dead volume and the stationary phase volume).  $R$  is the gas constant and  $T$  the absolute temperature,  $p^\circ$  and  $\gamma_S^\infty$  are, respectively, the solute's vapor pressure and infinite dilution activity coefficient in solvent  $S$  at temperature  $T$ ; and  $v_s$  denotes the solvent molar volume at the same temperature.

When the enantiomer  $X$  is injected in a column containing different concentrations of the selector  $A$  dissolved in the achiral solvent  $S$ , the equilibrium for the  $XA$ -complex formation is:



$$K_{XA}^\circ = \frac{a_{XA}}{a_X a_A} \cong \frac{m_{XA}}{m_X a_A} \quad (2)$$

where  $K_{XA}^\circ$  represents the thermodynamic association constant between enantiomer and CS,  $a_i$  represents the activity for species  $i$  with the convention that  $a_i$  approaches to concentration at infinite dilution. Under analytical chromatographic conditions the activities of the solute and the complex can be replaced by molal concentrations ( $m_i$ ) since those species are infinitely diluted. For practical reasons, the equilibrium would also be expressed by the stoichiometric association constant  $K_{XA}$  ( $= K_{XA}^\circ \gamma_A$ ), where  $\gamma_A$  denotes the CS activity coefficient.

Enantiomer retention in these columns is related to an apparent association constant,  $K_{app}$ , as follows:

$$K_{app} = k \times \beta = \frac{RT}{\gamma_{S+A}^\infty p^\circ v_{A+S}} (1 + K_{XA} m_A) \quad (3)$$

where  $k$  represents the retention factor for the enantiomer in the column containing the CS at concentration  $m_A$  and phase ratio equal to  $\beta$ . The solute activity coefficient in the solvent mixture  $S+A$  is denoted as  $\gamma_{S+A}^\infty$ . Similarly, the molar volume of the mixture,  $v_{S+A}$ , would be different from that of the pure solvent. Eq. (4) results from combining Eqs. (1) and (3):

$$K_{app} = K_L^\circ \frac{\gamma_S^\infty v_S}{\gamma_{S+A}^\infty v_{A+S}} (1 + K_{XA} m_A) = K_L^{\circ,*} (1 + K_{XA} m_A) \quad (4)$$

In Eq. (4), the constant  $K_L^{\circ,*}$  is equal to  $K_L^\circ$  if the ratio  $\gamma_S^\infty v_S / \gamma_{S+A}^\infty v_{A+S}$  equals 1. Similarly, a plot of  $K_{app}$  as a function of  $m_A$  is a straight line only if  $\gamma_{S+A}^\infty$  and  $v_{S+A}$  do not depend on  $m_A$ , but rather bear a linear relationship to CS molality. An assumption made here is that there are no synergistic effects between the achiral polysiloxane and the chiral selector.

Now, for any enantiomeric pair, the thermodynamic enantioselectivity,  $\alpha_{D/L}$ , is defined by the ratio  $K_{DA}^\circ / K_{LA}^\circ$ , which value is equivalent to the ratio between stoichiometric complex-formation constants  $K_{DA} / K_{LA}$ , where arbitrarily a stronger interaction between the D-enantiomer and the CS has been considered. The estimation of  $\alpha_{D/L}$  is possible only if these complex-formation constants can be measured. The usual and more accessible ratio between retention

factors for both enantiomers  $k_D/k_L$  will lead to an apparent enantioselectivity,  $\alpha_{D/L,app}$ :

$$\alpha_{D/L,app} = \frac{(1 + K_{DA} m_A)}{(1 + K_{LA} m_A)} \quad (5)$$

which value is always smaller than the true enantioselectivity, and the consequent apparent enantioselectivity factor would approach the true enantioselectivity only if ( $1 \ll K_{XA} m_A$ ).

The above treatment was independent of reference solutes; the apparent constants can be obtained from the measurements of retention factors of symmetric peaks in chiral columns of known phase ratios at each temperature.

## 3. Experimental

### 3.1. Instrumentation and materials

Chromatographic measurements were performed in an HP6890 (Agilent, Palo Alto, CA, USA) gas chromatograph equipped with flame ionization detection and manual injection. Split injection was used and the split ratio was kept at 1:100. The solute retention times were acquired with the software Clarity (DataApex, Czech Republic).

Fused silica tubing capillary of 250  $\mu\text{m}$  i.d. was provided by MicroQuartz (München, Germany), OV-1701 (5% cyanopropyl, 7% phenyl) was purchased to Supelco (Bellefonte, PA, USA), and octakis-(3-*O*-butanoyl-2,6-di-*O*-pentyl)- $\gamma$ -cyclodextrin (LIPODEX-E) was obtained from Cyclolab Ltd. (Budapest, Hungary). For comparison, we used a commercial Lipodex E column, 25 m  $\times$  250  $\mu\text{m}$  i.d., bought from Macherey-Nagel (Macherey-Nagel GmbH & Co. KG, Düren, Germany).

The racemic solutes were obtained from either, Aldrich–Sigma (St. Louis, MO, USA) or Fluka (Ronkonkoma, NJ, USA). Ethyl chloroformate (97%) and trifluoroacetic anhydride (>99%) were purchased from Aldrich and Fluka, respectively.

Chemical waste was delivered for a proper residual treatment.

### 3.2. Density measurements

A 2-mL Guy-Lussac pycnometer was employed to measure stationary phase densities. The pycnometer was initially calibrated within the range between 30 and 130 °C by using high purity *n*-tetradecane whose densities were taken from literature [10]. Next, the densities of pure OV-1701 and of a mixture containing 10% (w/w) CS at temperatures between 30 and 100 °C were measured. The obtained density values were then fitted to the following two polynomial equations:

$$\rho_{OV1701}(\text{g mL}^{-1}) = 1.297(\pm 0.032) - 0.0010(\pm 0.0002)T + 2.7(\pm 1.7) \times 10^{-7} T^2, \quad R^2 = 0.9998, \quad \text{s.e.} = 0.0004 \quad (6)$$

$$\rho_{10\%CS/OV1701}(\text{g mL}^{-1}) = 1.19(\pm 0.13) - 0.00020(\pm 0.00008)T - 1.1(\pm 1.0) \times 10^{-6} T^2, \quad R^2 = 0.9991, \quad \text{s.e.} = 0.0007 \quad (7)$$

where  $T$  represents the temperature in degrees Kelvin. The data showed that the density of the mixture is slightly larger than that of pure polysiloxane at all temperatures.

The densities of the two mixtures with the higher CD contents were estimated by extrapolation.

### 3.3. Column coating

Capillaries of 20 m in length without any surface pretreatment were prepared by a static coating procedure detailed elsewhere

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