Drug Development and Industrial Pharmacy, 26(10), 1111–1114 (2000)

COMMUNICATION

Determination of the Stability Constants in Alkanol/α-Cyclodextrin Mixed System

Yoshihiro Saito,* Kaname Hashizaki, Hiroyuki Taguchi, Kazuo Tomono, Hiroko Goto, and Naotake Ogawa

College of Pharmacy, Nihon University, 7-7-1 Narashinodai, Funabashi-shi, Chiba 274-8555, Japan

ABSTRACT

The simultaneous determination of the stability constants for inclusion of alkanols with α-cyclodextrin (α-CD) was investigated in a mixed alkanol system using static head-space gas chromatography (SHSGC). The 1:1 stability constants obtained were in fair agreement with those obtained previously using other methods. The time required for determination of the stability constant was markedly reduced using this simultaneous SHSGC method.

Key Words: *Alkanols; Complexes; α-Cyclodextrin; Mixed system; Stability constant.*

INTRODUCTION

We recently proposed new methods using static head-space gas chromatography (SHSGC) for determination of the stability constant for the cyclodextrin (CD) complex (1,2). Those methods have been applied successfully to determine the stability constants for the benzene derivatives/α-CD and alkanediols/α-CD complexes. Furthermore, we applied this SHSGC technique to fragrance material/2-hydroxypropyl-β-CD complexes in a mixed fragrance materials system and succeeded in the simultaneous determination of the stability constants (3). This method is called the *simultaneous SHSGC method*. However, the accumulation of additional information is required for further corroboration of the simultaneous SHSGC method.

In the present study, we investigated the determination of the stability constants for alkanol/α-CD complexes in a mixed alkanol system using the simultaneous SHSGC method.

EXPERIMENTAL

Materials

Reagent-grade 1- and 2-alkanols were purchased from Tokyo Kasei Kogyo Company, Limited, and used without further purification. The α-CD was provided by Ni-

* To whom correspondence should be addressed. Fax: +81-47-465-5865. E-mail: ysaito@pha.nihon-u.ac.jp

hon Shokuhin Kako Company, Limited, and was used after vacuum drying. Distilled water per injection JP was obtained from Ohtsuka Pharmacy Company, Limited.

Sample Preparation

Various amounts of an equimolar mixture of 1- and 2-alkanols were added to aqueous solution (10 g) with and without 10 mmol kg^{-1} α-CD weighed into 19.5-ml head-space vials. The sample solutions were sealed using silicone septa and aluminum foil. The vials were then thermostated at 25°C ± 0.1°C and shaken overnight prior to analysis.

Gas Chromatographic Analysis

After equilibrium was established, 400 μl of the alkanol vapor from above the solution was drawn from the vial using a gas-tight syringe. This sample was then analyzed using a gas chromatograph (GC; GC-14B, Shimadzu Co., Kyoto, Japan) equipped with a flame-ionization detector with a 1 m × 3 mm i.d. glass column packed with polyethylene glycol 20M (PEG-20M). The injection and detection temperatures were maintained at 200°C, and the column temperature was 80°C. Nitrogen was used as the carrier gas, and the flow rate was kept at 20

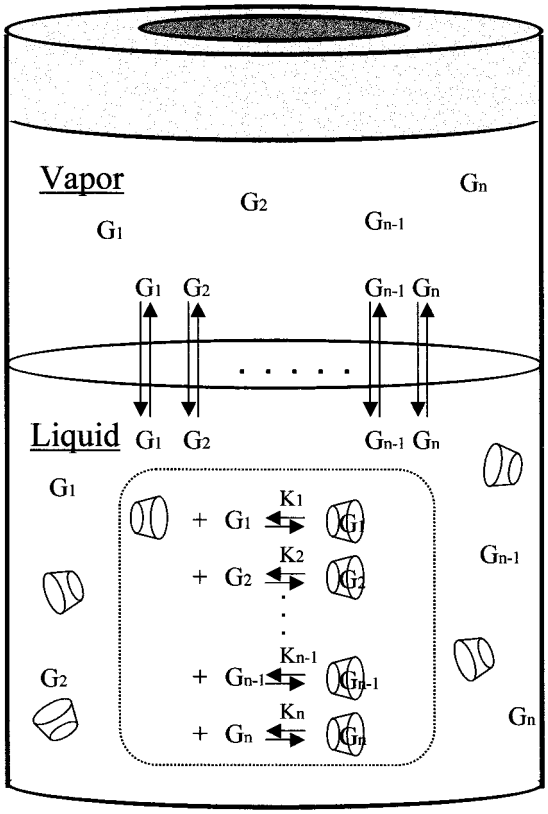

Figure 1. Schematic illustration of the simultaneous SHSGC method.

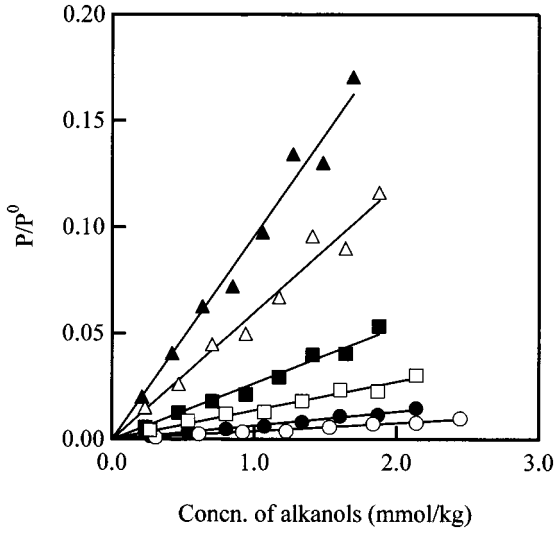

Figure 2. Plots based on Henry's law for mixed alkanols in aqueous solution. ○, 1-pentanol (r = 0.9902); □, 1-hexanol (r = 0.9828); △, 1-heptanol (r = 0.9620); ●, 2-hexanol (r = 0.9916); ■, 2-heptanol (r = 0.9870); ▲, 2-octanol (r = 0.9873).

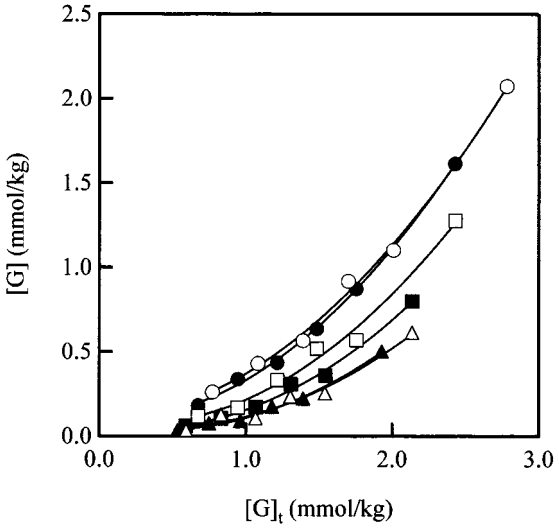

Figure 3. Best-fit curves for alkanol/α-CD complexes based on Eq. 4. ○, 1-pentanol; □, 1-hexanol; △, 1-heptanol; ●, 2-hexanol; ■, 2-heptanol; ▲, 2-octanol.

ml/min. The area of each peak was measured using a Shimadzu Chromatopac C-R 6A integrator.

RESULTS AND DISCUSSION

Theoretical

Figure 1 shows the proposed mechanism of the simultaneous SHSGC method. There are two equilibria in the volatile guests (G_n, $n = 1, 2, \ldots$)/CD/water system: (*a*) Each guest included in CD was in equilibrium with each free guest in the solution, and (*b*) each free guest was in equilibrium with each monomeric guest in the vapor above the solution. The guests shared the CD corresponding to their stability constants *K* based on the assumption that no complexes are formed except binary complexes that do not interfere with one another in the solution. If each guest in the vapor is separated and determined by GC, in principle, the stability constants can be evaluated using this method. The assumption was that the equilibrium between a guest component G_i and CD involved a 1:1 complex, as shown in Eq. 1:

$$G_i + \mathrm{CD} \overset{K_i}{\leftrightarrow} G_i - \mathrm{CD} \tag{1}$$

Stability constant K_i for a 1:1 complex is defined by Eq. 2:

$$K_i = \frac{[G_i - \mathrm{CD}]}{[G_i][\mathrm{CD}]} \tag{2}$$

where $[G_i]$ and [CD] denote the concentrations of the free solutes.

[Gi − CD] denotes the complex concentration. The mass balance of G_i in aqueous solution is represented by Eq. 3:

$$[G_i]_t = [G_i] + [G_i - \mathrm{CD}] \tag{3}$$

where $[G_i]_t$ is the total concentration of G_i in aqueous solution. The $[G_i]_t$ after equilibrium was determined by subtracting the number of moles of G_i in the vapor calculated using the ideal gas equation from the total amount of G_i added to the vial. Substituting Eq. 2 into Eq. 3,

$$[G_i] = \frac{[G_i]_t}{1 + K_i[\mathrm{CD}]} \tag{4}$$

$[G_i]_t$ is known, and $[G_i]$ can be obtained from a linear relationship according to Henry's law (Eq. 5) for the solution in the absence of CD (4):

$$P_i = H_i x_i \tag{5}$$

where P_i is the partial pressure of G_i over the solution, H_i is Henry's constant of G_i, and x_i is the molar fraction of G_i in the solution. Then, Eq. 5 becomes

$$P_i/P_i^0 = \gamma_i^\infty x_i \tag{6}$$

where

$$H_i = \gamma_i^\infty P_i^0 \tag{7}$$

in which γ_i^∞ is the limiting activity coefficient, and P_i^0 is the vapor pressure of G_i in the pure state. The ratio of P_i and P_i^0 is equal to the ratio of the integrated GC peak areas, corresponding to the GC peaks obtained from the head space of G_i in the solution and of its pure state.

The [CD] in Eq. 4 can also be determined from the mass balance of CD by Eq. 8:

$$[\mathrm{CD}] = [\mathrm{CD}]_t - [G - \mathrm{CD}]_t \tag{8}$$

where $[\mathrm{CD}]_t$ is the total concentration of CD that is known. $[G - \mathrm{CD}]_t$ is the total concentration of the com-

Table 1

Comparison of Stability Constants for Alkanol/α-Cyclodextrin Complexes

Alkanols	This Work[a] *K* (kg/mol)	Ref. 5 *K* (L/mol)	Ref. 6 *K* (kg/mol)
1-Pentanol	188 ± 28	324	275 ± 15
1-Hexanol	509 ± 68	891	379 ± 51
1-Heptanol	1586 ± 174	2291	—
2-Hexanol	331 ± 34	355	285 ± 13
2-Heptanol	1215 ± 104	—	—
2-Octanol	2153 ± 197	1413	—

[a] The values represent the mean ± SD.

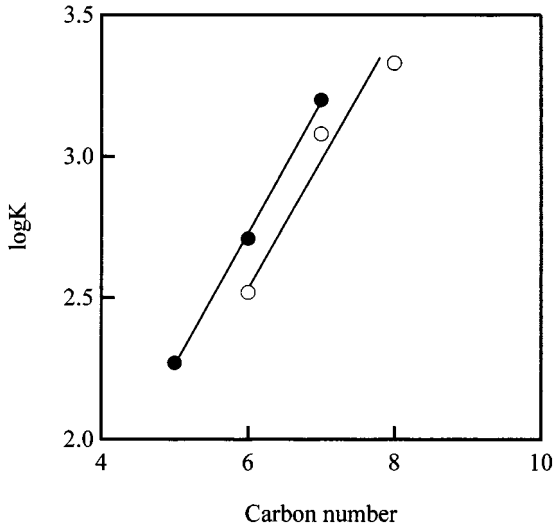

Figure 4. Effects of carbon number on stability constants for alkanol/α-CD complexes. ●, 1-alkanols ($r = 0.9995$); ○, 2-alkanols ($r = 0.9624$).

plex for all guests and is also calculated from the sum of each complex obtained from Eq. 3.

$$[G - \mathrm{CD}]_t = \sum_{i=1}^{n} [G_i - \mathrm{CD}] \quad (9)$$

Therefore, the stability constants for each guest can be estimated by a nonlinear least-squares fit using Eq. 4.

Stability Constant

We were able to make a quantitative separation of alkanol vapor above the solution containing the mixed alkanols by GC. Figure 2 shows the relationship between P/P^0 and concentrations of each alkanol for a mixed alkanol solution in the absence of α-CD based on Eq. 6. The plots gave straight lines in accordance with Henry's law for each alkanol. These straight lines were used to evaluate $[G_i]$ in the presence of α-CD.

Figure 3 shows the plots according to Eq. 4 for each 1-alkanol/α-CD and 2-alkanol/α-CD system together with the calculated curves that gave the best fit of the experimental data. The theoretical values agreed well with the experimental values (data points) for each alkanol. The findings shown in Fig. 3 also suggest that the stoichiometry of the complexes between alkanol and α-CD was 1:1. The apparent stability constants K determined by this method are summarized together with standard deviations and are compared with the previously reported values in Table 1. The K values determined in this study are in reasonable agreement with those obtained from previous reports (5,6). The K values were plotted as log K against total number of carbon atoms of the alkanols in Fig. 4. The plots for a homologous series of the straight-chain alkanols gave approximately straight lines, which increased with the increasing carbon number of the alkanols. Accordingly, this supports the idea that the cavity of α-CD accommodates the hydrophobic moiety of alkanols. In addition, it was also shown that the affinity of the 1-alkanols toward α-CD was higher than that of 2-alkanols, which suggests that the hydroxyl group of alkanols becomes a hindrance factor with their inclusion.

CONCLUSIONS

In this study, the stability constants for inclusion complexes of alkanols with α-CD were determined simultaneously using the simultaneous SHSGC method. It is very important to determine the K value for the 1:1 inclusion complex because most guests form 1:1 inclusion complexes with CD. This method is suggested as useful for the determination of the stability constant, particularly in the case of 1:1 stoichiometry. In addition, it is more advantageous than the conventional method because the experimental time required for the determination of the stability constant can be drastically shortened.

REFERENCES

1. Y. Saito, K. Yoshihara, I. Tanemura, H. Ueda, and T. Sato, Chem. Pharm. Bull., 45, 1711 (1997).
2. K. Yoshihara, I. Tanemura, Y. Saito, H. Ueda, and T. Sato, Chem. Pharm. Bull., 45, 2076 (1997).
3. Y. Saito, I. Tanemura, H. Ueda, and T. Sato, Chem. Pharm. Bull., 46, 1777 (1998).
4. B. V. Ioffe and A. G. Vitenberg, *Head-Space Analysis and Related Methods in Gas Chromatography*, John Wiley and Sons, New York, 1984, p. 13.
5. Y. Matui and K. Mochida, Bull. Chem. Soc. Jpn., 52, 2808 (1979).
6. S. Andini, G. Castronuovo, V. Elia, and E. Gallotta, Carbohydr. Res., 217, 87 (1991).