



# Determination of Stability Constants for Alkanol/ $\alpha$ -Cyclodextrin Inclusion Complexes using the Surface Tension Method

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**Abstract.** The stability constants for the inclusion of alkanols with  $\alpha$ -cyclodextrin ( $\alpha$ -CD) in aqueous solution have been determined using the surface tension method. Data analyses assuming 1 : 1 stoichiometry were applied to estimate the stability constants of these complexes. The stability constants obtained using this method were in reasonable agreement with the corresponding values in the literature. Chemically modified  $\alpha$ -CDs could not be used in this method because those CDs themselves have surface activity. In addition, the relation between the stability constants and the carbon number of alkanols is discussed.

**Key words:** alkanols,  $\alpha$ -cyclodextrin, surface tension, stability constant, inclusion complexes

## 1. Introduction

The stability constant is of fundamental importance in understanding interactions in guest/cyclodextrin (CD) systems. The stability constant has mainly been determined using spectroscopic methods such as absorption spectroscopy and fluorescence spectroscopy [1–2]. It is difficult, however, to determine directly the stability constant using these spectroscopic methods if the systems have no chromophoric groups. Alkanols, except for aromatic alkanols, are the best known examples of such systems. For such systems, other methods such as competitive spectrophotometry [3], NMR [4] and calorimetry [5] etc. have been used for determination of stability constants. In addition, some new methods such as static head-space gas chromatography [6], freezing point depression [7] and ultrafiltration [8] methods have been recently developed for determination of stability constants. The surface tension measurement is also one of the new methods and has proved suitable for

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studying the interaction of guest and CD [9–11]. We have also proposed a method using the surface tension technique for determination of stability constant of surfactant/CD complexes [12–13]. However, to date, this technique has been applied to surfactant alone as guest. Fortunately, most organic compounds have surface activity [14], therefore, it is possible to investigate whether the surface tension technique can be applied for organic compounds in addition to surfactants.

In this study, we examined the applicability of the surface tension method for determining the stability constants of complexes of various alkanols with  $\alpha$ -CD. Also, the relative strength of the complex formation of alkanols and  $\alpha$ -CD was compared.

## 2. Experimental

### 2.1. MATERIALS

Alkanols of reagent grade were purchased from Tokyo Kasei Kogyo Co., Ltd. and used without further purification. Naturally occurring  $\alpha$ -cyclodextrin ( $\alpha$ -CD) was provided by Nihon Shokuhin Kako Co. Ltd.. Chemically modified  $\alpha$ -CDs (2-hydroxypropyl- $\alpha$ -cyclodextrin (HP- $\alpha$ -CD) with an average substitution degree of 4.1 and hexakis (2,6-di-O-methyl)- $\alpha$ -cyclodextrin (DM- $\alpha$ -CD) with an average substitution degree of 12) and branched  $\alpha$ -CD (6-O- $\alpha$ -D-glucosyl- $\alpha$ -cyclodextrin (G<sub>1</sub>- $\alpha$ -CD) with an average substitution degree of 1) were obtained from Wako Pure Chemical Industries, Ltd. All  $\alpha$ -CDs were used after drying in a vacuum. Distilled water per injection JP (Japanese Pharmacopoeia) was obtained from Ohtsuka Pharmacy Co., Ltd.

### 2.2. MEASUREMENTS

Surface tension measurements were made using a Wilhelmy type surface tensiometer (Kyowa Interface Science Co., Model CBVP-A3) within a precision of  $\pm 0.2$  mN m<sup>-1</sup>. All surface tension measurements were made at  $25 \pm 0.1$  °C.

## 3. Results and Discussion

The stability constant for a surface active compound/CD complex can be quantified assuming that both CD and the complex are non-surface active [9–13]. First, an attempt was made to measure the surface tension of some typical  $\alpha$ -CDs, which are often used in the field of CD studies. Figure 1 shows the effects of various  $\alpha$ -CDs on the surface tension. The surface tension values of HP- $\alpha$ -CD and DM- $\alpha$ -CD were remarkably decreased with an increase in the concentration, indicating that CDs themselves have surface activity. However,  $\alpha$ -CD was non-surface active and G<sub>1</sub>- $\alpha$ -CD barely indicated surface activity. Consequently, it was clear that the natural  $\alpha$ -CD and the branched  $\alpha$ -CD can be used to determine the stability constant using the surface tension method. We used  $\alpha$ -CD as a host in this study. The second condition

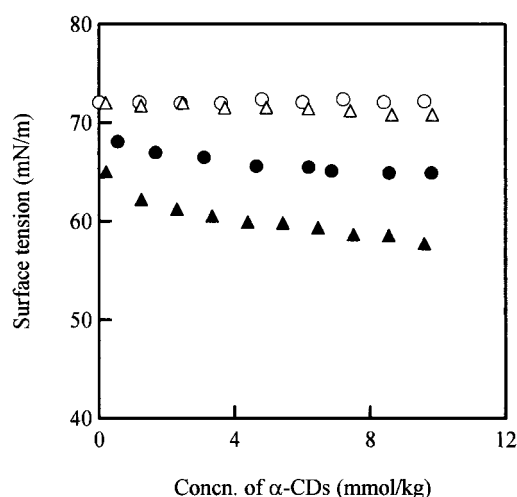


Figure 1. Surface tension results for various  $\alpha$ -CDs at 25 °C:  $\circ$ ,  $\alpha$ -CD;  $\Delta$ , G1- $\alpha$ -CD;  $\bullet$ , HP- $\alpha$ -CD;  $\blacktriangle$ , DM- $\alpha$ -CD.

for the application of the surface tension method is that the complex formed is non-surface active. The systems used in this study satisfied these conditions as described in the latter half of this report.

Figure 2 shows the results of the surface tension for 1-hexanol and cyclohexanol aqueous solutions in the presence and in the absence of added  $\alpha$ -CD as examples. The addition of  $\alpha$ -CD to the 1-hexanol and cyclohexanol aqueous solutions increased the surface tension compared with no  $\alpha$ -CD, suggesting that the thermodynamic activities of 1-hexanol and cyclohexanol were decreased by formation of inclusion complexes with  $\alpha$ -CD. Since the concentration dependence of the surface tension for 1-hexanol and cyclohexanol in the absence of  $\alpha$ -CD gave straight lines, the free concentrations of 1-hexanol and cyclohexanol in the presence of  $\alpha$ -CD can be obtained from these linear relationships. Similar results were observed for thirty alkanol systems. The stability constants ( $K$ ) were calculated using the following equation based on the assumption that a 1 : 1 complex was formed [15]:

$$[A] = \frac{-(K[\alpha - CD]_t - K[A]_t + 1) + \sqrt{(K[\alpha - CD]_t - K[A]_t + 1)^2 + 4K[A]_t}}{2K}, \quad (1)$$

where  $[A]_t$  and  $[\alpha - CD]_t$  are the total concentrations of alkanol and  $\alpha$ -CD, respectively, and these are known values.  $[A]$  denotes the free concentration of alkanol in the presence of  $\alpha$ -CD, obtained experimentally from the calibration curve between the surface tension and alkanol concentration in the absence of  $\alpha$ -CD, as described above. Therefore, the stability constant can be estimated from non-linear least squares treatment of  $[A]$  vs.  $[A]_t$ .

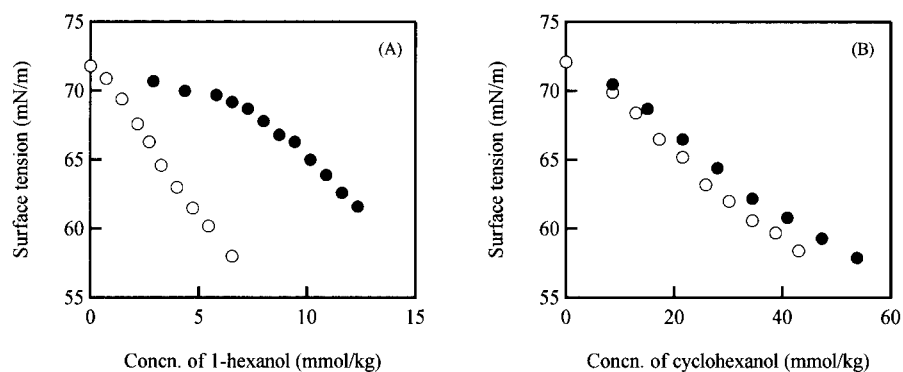


Figure 2. Surface tension results for 1-hexanol (A) and cyclohexanol (B) in the presence and absence of  $10 \text{ mmol kg}^{-1}$   $\alpha$ -CD at  $25^\circ\text{C}$ :  $\circ$ , without  $\alpha$ -CD;  $\bullet$ , with  $\alpha$ -CD.

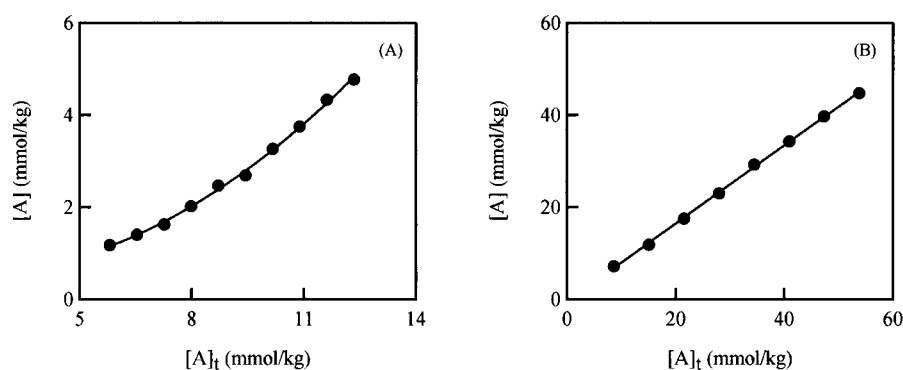


Figure 3. Plots of  $[A]$  vs.  $[A]_t$  for 1-hexanol (A) and cyclohexanol (B) at  $25^\circ\text{C}$ .

Figure 3 shows the plots of  $[A]$  vs.  $[A]_t$  for 1-hexanol and cyclohexanol together with the calculated curves, which gave the best fit of the experimental data. The theoretical values agreed well with the experimental values (data points) for each alkanol. The results shown in Figure 3 also suggest that the stoichiometry of the 1-hexanol/ $\alpha$ -CD and cyclohexanol/ $\alpha$ -CD complexes was 1 : 1. The same surface tension technique was applied to each of the thirty alkanol systems. The determined stability constants are summarized together with S.D. and are compared with the previously reported values in Table I. The S.D. values were derived from a single experiment consisting of a set of data points fitted to a model function by least-squares analysis [6]. The stability constant values determined in this study are in reasonable agreement with previously reported values except for 3-pentanol, 1-heptanol and 1-octanol. Due to a lack of stability constant data for these alkanols available in the literature, it is difficult at present to judge which is the more reliable. However, in comparison with the K values of other alkanols it appears that these previously reported values are too large.

*Table 1.* Comparison of stability constants for alkanol/ $\alpha$ -CD complexes

| Alkanols               | This work<br>(kg/mol) | Ref. 16<br>(L/mol) | Ref. 17<br>(kg/mol) |
|------------------------|-----------------------|--------------------|---------------------|
| 1-Butanol              | 93 $\pm$ 20           | 89                 | 100                 |
| 2-Butanol              | 21 $\pm$ 2            | 26                 | 28                  |
| 1-Pentanol             | 378 $\pm$ 25          | 324                | 275                 |
| 2-Pentanol             | 108 $\pm$ 8           | 135                | 101                 |
| 3-Pentanol             | 45 $\pm$ 2            | 87                 | 70                  |
| 3-Methyl-1-butanol     | 57 $\pm$ 4            | 74                 |                     |
| 1-Hexanol              | 698 $\pm$ 18          | 891                | 379                 |
| 2-Hexanol              | 412 $\pm$ 9           | 355                | 285                 |
| 3-Hexanol              | 159 $\pm$ 11          |                    | 156                 |
| 2-Methyl-2-pentanol    | 244 $\pm$ 5           |                    |                     |
| 3-Methyl-2-pentanol    | 152 $\pm$ 5           |                    |                     |
| 3,3-Dimethyl-1-butanol | 77 $\pm$ 5            |                    |                     |
| 4-Methyl-1-pentanol    | 151 $\pm$ 4           |                    |                     |
| 4-Methyl-2-pentanol    | 58 $\pm$ 3            | 55                 |                     |
| 1-Heptanol             | 1270 $\pm$ 35         | 2291               |                     |
| 2-Heptanol             | 713 $\pm$ 9           |                    |                     |
| 3-Heptanol             | 508 $\pm$ 8           |                    |                     |
| 4-Heptanol             | 379 $\pm$ 7           |                    | 188                 |
| 1-Octanol              | 3316 $\pm$ 75         | 6310               |                     |
| 2-Octanol              | 1973 $\pm$ 23         | 1413               |                     |
| 3-Octanol              | 942 $\pm$ 11          |                    |                     |
| 4-Octanol              | 543 $\pm$ 5           |                    |                     |
| 1-Nonanol              | 6706 $\pm$ 129        |                    |                     |
| 2-Nonanol              | 3576 $\pm$ 44         |                    |                     |
| 3-Nonanol              | 2134 $\pm$ 24         |                    |                     |
| 4-Nonanol              | 1002 $\pm$ 12         |                    |                     |
| 5-Nonanol              | 684 $\pm$ 16          |                    |                     |
| Cyclobutanol           | 23 $\pm$ 2            | 39                 |                     |
| Cyclopentanol          | 40 $\pm$ 5            | 46                 |                     |
| Cyclohexanol           | 50 $\pm$ 8            | 65                 |                     |

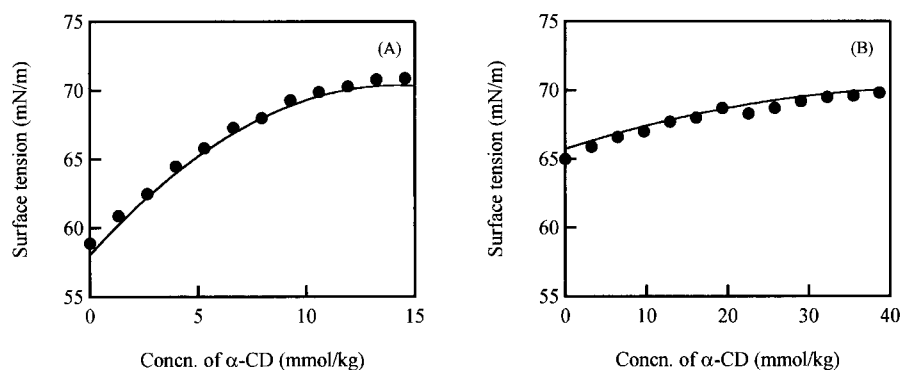


Figure 4. Surface tension results for 6 mmol kg<sup>-1</sup> 1-hexanol (A) and 20 mmol kg<sup>-1</sup> cyclohexanol (B) in the presence of variable concentrations of added  $\alpha$ -CD at 25 °: Symbols represent experimental data and the lines conform to the model.

Figure 4 shows the influence of adding  $\alpha$ -CD to aqueous solutions containing a fixed 1-hexanol or cyclohexanol concentration as examples. The surface tension values increased with an increase in  $\alpha$ -CD concentrations and gradually approached the surface tension value of pure water. This demonstrates that alkanols and  $\alpha$ -CD form inclusion complexes, and the inclusion complexes do not have any surface activity. The curves drawn in Figure 4 represent the surface tension values predicted by the model, calculated using the stability constants reported in Table I. Although the findings appear to differ a little from the values predicted by the model, the deviations between the model predictions and the experimental surface tension values were no more than 0.6 mN m<sup>-1</sup> in the concentration regions examined. This suggests that a reasonable correlation of measurements was obtained in each case.

Figure 5 shows the plots of the K values vs. carbon number of alkanols. The plots for a homologous series of the straight chain alkanols and the cyclic alkanols gave approximately straight lines, which increase with increasing carbon number of the alkanols. In addition, the refractive points exist around the carbon numbers corresponding to 5 for 1-alkanols, 6 for 2-alkanols and 7 for 3-alkanols. The same finding for 1-alkanols/ $\alpha$ -CD systems has already been recognized in the relationship between stability constants and partition coefficients of 1-alkanols in diethyl ether-water [16]. This is because a part of the apolar group in the straight alkyl chain over 6 carbons protrudes from the  $\alpha$ -CD cavity to bulk [16]. Also, these straight lines in the order of 1-alkanols, 2-alkanols, 3-alkanols and 4-alkanols suggest that the hydroxyl group of alkanols becomes a hindrance factor of the inclusion. The stability constants of cyclic alkanols and branched alkanols were significantly smaller than those of 1-alkanols with the same carbon number. The reason for this may be that these alkanols are much bulkier than straight chain alkanols.

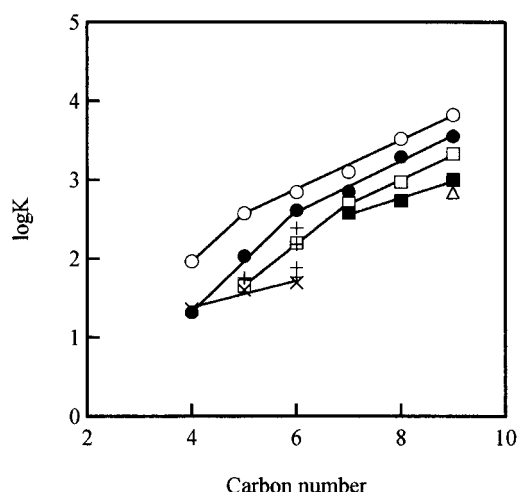


Figure 5. Plots of  $\log K$  vs. carbon number for alkanol/ $\alpha$ -CD systems: ○, 1-alkanols; ●, 2-alkanols; □, 3-alkanols; ■, 4-alkanols; △, 5-alkanols; ×, cycloalkanols; +, branched alkanols.

#### 4. Conclusions

A study was made of the determination of the stability constants of thirty alkanol/ $\alpha$ -CD systems using a surface tension method. In this study, we showed that the surface tension method can determine the stability constants for alkanol/ $\alpha$ -CD systems simply and accurately. Consequently, this method is applicable to guests which show no change in the spectra such as alkanols other than aromatic alkanols. However, the surface tension method has a disadvantage as do other methods, in that, its application is difficult for chemically modified CDs such as HP- $\alpha$ -CD and DM- $\alpha$ -CD which display surface activity.

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