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Association of Alcohol-Cyclodextrin in Aqueous Medium Determined by Headspace Gas Chromatography

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It is well-known that cyclodextrins (CyD's) form inclusion complexes with alcohols (guests) in an aqueous medium. Such complex formations have been studied by various techniques, which involve NMR¹, calorimetric²⁻⁷, spectrophotometric⁷⁻⁹, and ultrasonic relaxation¹⁰ methods. These studies, however, were exclusively concerned with α - and β -CyD's. To our knowledge, no data have been reported for γ -CyD. *n*-Alcohols associate with α -CyD more strongly than with β -CyD. These guests are closely fitted to the relatively small α -CyD cavity, whereas they are too small in size to be in close contact with the relatively large cavity of β -CyD.⁸ Then, it is expected that *n*-alcohols should associate with γ -CyD more weakly than with β -CyD, because the cavity size of γ -CyD is still larger than β -CyD.

Despite weak association of *n*-alcohols with γ -CyD, these guests play an important role in complexations of γ -CyD with a certain guest of relatively large molecular size, such as pyrene.¹¹ Accurate knowledge of alcohol-CyD association is also needed in the reversed-phase LC, where CyD's have been used as a modifier to improve separation by their molecular recognizing ability.¹²

Headspace GC is a useful technique to study partition of volatile solutes between gaseous and aqueous phases. This technique is of two types: one is "static headspace", in which the vapor phase is directly injected into a GC column and the other is "enriched headspace", which requires trapping of volatile components onto an adsorbent prior to GC injection. The aim of the present work is to demonstrate that static headspace GC is simple and suitable for determining association constants of alcohol-CyD in aqueous medium. This report is the first to present the association constants of alcohols with γ -CyD.

Experimental

n-Alcohols (C₄ to C₉) and 2-pentanol (Wako Pure Chemical Co.) of the highest commercially available purity were used without further purification. α -, β -, and γ -CyD's of guaranteed grade (Nacalai Tesque Co.), dried over phosphorus pentoxide under vacuum, were used as received. Deionized distilled water was used throughout the experiments.

A known initial concentration of alcohol solution of 20 ml was prepared in a bottle of 27-ml capacity in the absence and presence of CyD of various concentrations. The bottle was sealed with a silicone rubber septum cap with PTFE liner facing toward the bottle headspace. At least three bottles were used for a single sample solution. The bottles were immersed in a 25.0±0.1°C water bath for one day with occasional gentle swirling. After equilibration, vapor samples (200 μ l) were withdrawn from the headspace of the sealed bottles with a gas-tight syringe (Shimadzu HSS-2B) and directly injected into a Shimadzu GC-14A gas chromatograph. The GC conditions were as follows: a 3.2 mm×2.1 m column packed with SE-30 (60 - 80 mesh), a FID detector, and a operating temperature of 120 - 160°C.

Results and Discussion

Calibration curves were prepared in the absence of CyD using alcohol solutions of five different concentrations in the range of the following highest alcohol concentration (10⁻³ M) to its one tenth or one twentieth (in the case of 1-nonanol, C₉): C₄(9.96), C₅(5.08), 2-pentanol(4.97), C₆(5.93), C₇(4.22), C₈(2.04), and C₉(0.809). A good linear relationship was observed for each alcohol between the chromatogram peak area, which corresponds to the alcohol vapor pressure in the headspace, and the total alcohol concentration. This indicates, as previous workers pointed out^{13,14}, that Henry's law holds for aqueous alcohol solutions. That is,

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$$P=K_H X, \quad (1)$$

where K_H is the Henry's law constant in Pa. As a matter of convenience for the present purpose, we use the peak area (A) for the alcohol vapor pressure (P) and the molar concentration of alcohol ($[Alc]$) in the aqueous phase for the mole fraction concentration (X). Then, Eq. (1) becomes

$$A=K'_H [Alc], \quad (2)$$

where K'_H is the apparent Henry's law constant.

Assuming 1:1 (alcohol:CyD) association, the total (initial) alcohol concentration ($[Alc]_0$) in a CyD solution and the total CyD concentration ($[CyD]_0$) are expressed as follows:

$$[Alc]_0=[Alc]+[CyD \cdot Alc] \quad (3)$$

and

$$[CyD]_0=[CyD]+[CyD \cdot Alc], \quad (4)$$

where $[CyD \cdot Alc]$ is the concentration of the associated complex. Then, an association constant (K) is derived using an equilibrium concentration of each species as follows:

$$K=\frac{[CyD \cdot Alc]}{[CyD][Alc]} \\ =\frac{([Alc]_0-[Alc])}{[CyD][Alc]}, \quad (5)$$

where $[CyD]$ is equal to $\{[CyD]_0-([Alc]_0-[Alc])\}$. Combining Eq. (5) with Eq. (2) yields

$$A_0/A=1+K[CyD], \quad (6)$$

where A_0 is the peak area at $[Alc]_0$. Equation (6) indicates that A_0/A vs. $[CyD]$ plots give a straight line, the slope of which corresponds to K . Here, $[CyD]$ can be estimated by Eq. (7):

$$[CyD]=\frac{[Alc]_0(A_0/A)-A_0}{K'_H}, \quad (7)$$

where K'_H is the slope of the calibration curve.

Some examples of experimental results are given in Table 1. For all of the alcohol-CyD combinations studied in this work, good linear relationships were observed between A_0/A and $[CyD]$. The least-squares method was applied to determine K . The results are summarized in Table 2, where the related data reported in the literature are also listed. The present K values for α - and β -CyD's are in accordance with the literature data, though the data themselves exhibit some scatter. Reasonable agreements are observed between our results and those^{8,9} determined spectrophotometrically.

It is noteworthy that for the corresponding alcohols, the association constants of γ -CyD are about one order of magnitude smaller than those of β -CyD; the K values of β -CyD are two to seven times smaller than those

Table 1 Some examples of experimental results

$[CyD]_0/10^{-3}$ M	A_0/A	$[Alc]/10^{-3}$ M	$[CyD]/10^{-3}$ M
1-Butanol- α -CyD, $[Alc]_0=9.96 \times 10^{-3}$ M			
6.00	1.316	7.57	3.61
12.0	1.660	6.00	8.04
18.0	2.102	4.74	12.8
24.0	2.532	3.94	18.0
30.0	2.974	3.35	23.4
36.0	3.338	2.99	29.0
1-Butanol- β -CyD, $[Alc]_0=4.99 \times 10^{-3}$ M			
1.50	1.010	4.94	1.45
3.50	1.026	4.87	3.38
5.50	1.050	4.75	5.26
7.50	1.076	4.64	7.15
9.50	1.121	4.50	9.01
1-Butanol- γ -CyD, $[Alc]_0=5.07 \times 10^{-3}$ M			
20.0	1.042	4.86	19.8
35.0	1.063	4.77	34.7
50.0	1.080	4.70	49.6
65.0	1.106	4.59	64.5
80.0	1.144	4.43	79.4
95.0	1.193	4.25	94.2
1-Nonanol- α -CyD, $[Alc]_0=8.09 \times 10^{-4}$ M			
0.500	2.102	0.382	0.0730
1.00	5.545	0.141	0.332
1.50	11.21	0.0670	0.758
2.00	17.61	0.0410	1.23
1-Nonanol- γ -CyD, $[Alc]_0=8.00 \times 10^{-4}$ M			
2.00	1.181	0.678	1.88
4.00	1.476	0.543	3.74
6.00	1.726	0.464	5.66
8.00	1.995	0.402	7.60
10.0	2.272	0.350	9.55

of α -CyD. Such order of decreasing stability is compatible with the idea, proposed by Matsui and Mochida⁸, that the CyD cavity size is a dominant factor in complexation with n -alcohols.

The cross-section diameter of a straight-chain alcohol molecule (0.45 nm) is close to that of α -CyD cavity (0.5 nm). The cavity diameter of γ -CyD (0.85 nm), which is still larger than that of β -CyD (0.69 nm), is too large to accept an n -alcohol molecule suitably. The association constant of n -alcohol with the three types of CyD increases with an increase in an alkyl chain length. This is probably due to an increase in contact area between the host molecule and the CyD inner wall. It is interesting to compare the K value of n -alcohol with that of n -alkane¹⁵ of the same carbon number. The former is much larger than the latter for both α - and β -CyD's, while the two K values are almost comparable for γ -CyD. This means that stabilization through hydrogen bonding between n -alcohol and CyD does not work for γ -CyD.

As demonstrated by Tucker and Christian¹⁶, vapor pressure measurements are useful in estimating host-guest association, where volatile guests are concerned.

Table 2 Alcohol-CyD association constant at 25°C

Alcohol (Guest)	CyD (Host)	Association constant/M ⁻¹		
		This work (Correlation coefficient)		Literature
1-Butanol	α	81±1	(0.999)	89 ^a , 46±15 ^b , 82±1 ^c , 81 ^d , 161 ^e , 99.9 ^f , 79.7±2.5 ^g 17 ^a , 19±4 ^b , 25 ^c , 16±2 ^g , 17 ^h , 7±2 ⁱ
	β	14±1	(0.981)	
	γ	2.0±0.1	(0.979)	
1-Pentanol	α	291±3	(0.999)	324 ^a , 210±40 ^b , 245±1 ^c , 333 ^d , 333 ^e , 275 ^f 63.1 ^a , 140±40 ^b , 161 ^c , 62 ^h
	β	61.3±0.1	(0.997)	
	γ	3.3±0.4	(0.955)	
2-Pentanol	α	115±1	(0.999)	135 ^a , 105±9 ^b , 125±3 ^g , 101 ^j 30.9 ^a , 59±10 ^b , 32±11 ^g
	β	25±1	(0.993)	
	γ	3.1±0.1	(0.999)	
1-Hexanol	α	(8.6±0.2)×10 ²	(0.999)	891 ^a , 940±300 ^b , 702±1 ^c , 376 ^d , 379 ^j 219 ^a , 340±90 ^b , 1.9×10 ² ^h
	β	(2.6±0.1)×10 ²	(0.989)	
	γ	13±1	(0.976)	
1-Heptanol	α	(2.46±0.05)×10 ³	(0.999)	2.29×10 ³ ^a , 2700±900 ^b , 1163±1 ^c 708 ^a , 700±400 ^b , 6.2×10 ² ^h
	β	(9.85±0.09)×10 ²	(0.999)	
	γ	37±3	(0.973)	
1-Octanol	α	(4.82±0.06)×10 ³	(0.996)	6.31×10 ³ ^a , 7800±4600 ^b 1.48×10 ³ ^a , 2100±600 ^b , 1.6×10 ³ ^h
	β	(1.91±0.01)×10 ³	(0.996)	
	γ	67±4	(0.986)	
1-Nonanol	α	(1.34±0.01)×10 ⁴	(0.999)	3.4×10 ³ ^h
	β	(4.9±0.1)×10 ³	(0.998)	
	γ	141±2	(0.999)	

a. Ref. 8. b. Ref. 1. c. Ref. 5. d. Ref. 3. e. Ref. 4. f. Ref. 2. g. Ref. 6. h. Ref. 9. i. Ref. 10. j. Ref. 7.

They have studied the benzene-CyD system by measuring the change in vapor pressure of benzene in the absence and presence of CyD. Such measurements are troublesome and need a specially designed device; moreover, much attention should be paid to possible impurities with high volatility. Headspace GC, on the other hand, is simple and applicable to guests, the concentration of which in the gas phase is high enough to be detected by GC.

If the Henry's law constant, K_H , at 25°C is smaller than a critical value, 1.37×10^5 V/v Pa, the amount of solute in a v ml headspace vaporized from a V ml solution is less than 0.1% of the solute initially present in the solution; hence, there is no need to compensate for the solute which has escaped from the solution. In the present case, V and v being 20 and 7 ml, respectively, the critical value amounts to 3.91×10^5 Pa, while the K_H is at largest 1.7×10^5 Pa for 1-nonanol¹⁷, the most volatile alcohol studied.

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