

Volume Change on Complex Formation Between Anions and Cyclodextrins in Aqueous Solution

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Partial molal volume changes during complex formation between SCN^- , I^- , and ClO_4^- and α - and β -cyclodextrin have been determined by two independent methods of measurements; one based on density measurement and subsequent calculation of apparent molal volumes, the other on differentiating the association constants with respect to pressure. Results from the two methods are in good agreement.

Negative volume changes were observed for complex formation between the anions and α -cyclodextrin while zero or slightly positive values were observed for complex formation with β -cyclodextrin. The result is consistent with the idea that the anions do not become dehydrated as they form complexes with cyclodextrins.

KEY WORDS: Complex formation; association constant; partial molal volume; volume changes; dehydration; aqueous; cyclodextrins.

1. INTRODUCTION

Compounds that are able to form inclusion complexes with guest molecules or ions have received considerable attention. Macrocyclic polyethers (or crown ethers) are one such class of compounds known to form stable complexes with cations.⁽¹⁻³⁾ Another class of complex forming compounds are the cyclodextrins (or cycloamyloses). The cyclodextrins are cyclic oligosaccharides containing from 6 to 12 α -1,4-linked glycopyranose units. They form inclusion complexes with a number of different molecules and ions⁽⁴⁻⁶⁾ but contrary to crown ethers they form complexes with anions.^(7,8)

In previous papers we have presented partial molal volume data

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for complex formation between crown ethers and alkali and alkaline earth cations in aqueous solution.^(9,10) The ΔV° values of complex formation differed with the cation, but in all cases positive ΔV° values were observed. The results suggested some degree of dehydration of the cations as they entered the crown ether cavity.

It appeared interesting to extend this investigation to anion complex formation, and the cyclodextrins seemed a natural choice as complex forming agents. In this paper we thus present data for the partial molal volume changes of complex formation between some inorganic anions and two cyclodextrins; α -cyclodextrin containing 6 glycopyranose units and β -cyclodextrin containing 7.

The ΔV° of complex formation can be determined by at least two independent methods of measurement. First, the partial molal volumes of anions in the complexed and uncomplexed states at infinite dilution can be determined from density measurements. ΔV° is then calculated as the difference.⁽⁹⁾ The other method is based on the equation:

$$RT \left(\frac{\partial \ln K}{\partial P} \right)_T = -\Delta V^\circ \quad (1)$$

where K is the association constant of the complex. In order to use Eq. (1) the association constant must be determined as a function of pressure.

In this paper both methods of evaluating ΔV° of complex formation have been employed.

2. EXPERIMENTAL

α - and β -cyclodextrin were purified by the method of French *et al.*⁽¹¹⁾ Since the densities of aqueous solutions of purified and untreated cyclodextrins were not significantly different, the cyclodextrins were used as received. However Shahidiet *al.*⁽¹²⁾ have shown that both α - and β -cyclodextrin contain two water molecules per cyclodextrin molecule even after drying in an evacuated desiccator for two days. We repeated a Karl Fischer titration on our samples after two days and obtained the same results.

Water was distilled once to obtain a product with a specific conductivity of 1.0×10^{-6} S-cm⁻¹.

KSCN, NaClO₄, KI, and Na₂SO₄ were 'Baker analyzed'. NaClO₄ was dried in an evacuated desiccator for two days. KI was dried at

140°C and KSCN and Na₂SO₄ at 160°C. The molar conductivities at infinite dilution agreed with literature data⁽¹³⁾ within $\pm 0.1\%$ for all four inorganic salts.

The conductivities at atmospheric pressure were measured in a dilution cell, *i.e.* a 250 ml erlenmeyer flask to which an electrode compartment was sealed. At high pressures, pyrex glass cells were immersed in stainless steel vessels with hydraulic oil as the pressurizing medium. The cells were sealed with flexible rubber tubing making the pressure within the cell equal to the applied pressure. The cell constants were determined by using the data of Fuoss *et al.*^(14,15)

The conductivities were measured by a Wayne-Kerr autobalance bridge. The pressure was read by a Hottinger-Baldwin high pressure transducer (± 2 bar), and the temperature was kept within $\pm 0.01^\circ\text{C}$ as measured by a Hewlett-Packard quartz thermometer.

Densities were measured by a Paar densitometer (DMA 601) as previously described.⁽¹⁶⁾ The temperature was controlled to better than $\pm 0.005^\circ\text{C}$.

3. RESULTS

Between an anion (X^n) and cyclodextrins (CD) the following equilibrium is assumed:



On this basis Wojcik and Rohrbach⁽⁷⁾ have demonstrated that α , the fraction of anions in the uncomplexed state, can be calculated from conductivity measurements by the following equation:

$$\alpha = \frac{\Lambda - \Lambda(\text{MCDX})}{\Lambda(\text{MX}) - \Lambda(\text{MCDX})} \quad (3)$$

Λ is the measured molar conductivity of a solution containing both salt and cyclodextrin at specified concentrations. $\Lambda(\text{MX})$ is the molar conductivity of a solution of pure salt at the same concentration, and $\Lambda(\text{MCDX})$ is the molar conductivity of a hypothetical solution containing only the anion-cyclodextrin complex. The latter cannot be measured. However, Wojcik and Rohrbach⁽⁷⁾ have demonstrated that $\Lambda^\circ(\text{MCDX})$ can be estimated by using data for the diffusion coefficient of β -cyclodextrin. They obtained $\lambda_o(\text{CDX}^-) = 6.8 \text{ S-cm}^2\text{-mol}^{-1}$ for at 25°C and atmospheric pressure. At finite concentrations $\Lambda(\text{MCDX})$

was calculated from the square root law of Kohlrausch with the limiting slope equal to 79.1.

At higher pressures we have assumed that the following relation is valid:

$$[\lambda_o(\text{CDX}^-)/\lambda_o(\text{X}^-)]_p = [\lambda_o(\text{CDX}^-)/\lambda_o(\text{X}^-)]_{p=1} \quad (4)$$

Yet another correction must be made in order to use Eq. (3). The viscosity of the solution increases when cyclodextrin is added. The term Λ in Eq. (3) must be corrected for this viscosity increase. This can be done for instance by measuring the molar conductivity of NaClO_4 with and without cyclodextrin added. The SO_4^{2-} ion does not form complexes with α - or β -cyclodextrin to any significant extent, and the decrease in conductivity upon cyclodextrin addition can be ascribed to the viscosity increase. This correction method, previously used at atmospheric pressure,⁽⁷⁾ can be used at any other pressure.

Table I. Association Constants for the Complex Formation Between Anions and Cyclodextrin at Atmospheric Pressure and 25°C

Salt	α -cyclodextrin		β -cyclodextrin	
	This Work ^a	Lit. ^b	This Work	Lit.
KSCN	22.8	18.7	4.5	9.9 ^b
NaClO_4	30.6	28.9 ^c	24.5	26.7 ^d
KI	13.2	12.3	3.9	18.0 ^d

^aAverage of three determinations at 0.01, 0.015, and 0.02 molal; ^bRef. 7; ^cMeasured for KClO_4 ; ^dRef. 8.

In order to calculate α from Eq. (3) one has to rely on differences in conductivity between the various entities in the solution. These conductivities are all of the same order of magnitude, and may result in large error in α although the conductivities can be reproduced within $\pm 0.1\%$. The various assumptions and corrections mentioned above further adds to the error in α and consequently in the association constants. On this basis the agreement between our values and literature data, all presented in Table I, must be regarded as acceptable with the exception of complex formation between I^- and β -cyclodextrin. Eyring *et al.*⁽⁸⁾ report 18.0 from a spectral competitive inhibition mea-

surement while our conductivity measurements only yield 3.9.

The association constants of anion- α -cyclodextrin formation were determined at three different cyclodextrin concentrations, 0.1, 0.15, and 0.20*m*. The ionic strength was about 0.02 in all experiments. Only average values of the association constant are presented in Table I. The difference in α -cyclodextrin concentration did not produce association constants that differed by more than 2. Only one concentration of β -cyclodextrin, 0.015*m*, was used.

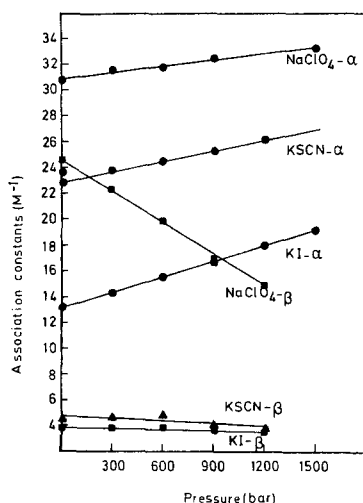


Fig. 1. Association constants of complex formation between the anions ClO_4^- , SCN^- , and I^- and α - and β -cyclodextrin in aqueous solution at 25°C.

The pressure dependence of the association constants are plotted in Fig. 1. Apparently there is a linear relationship in all cases.

Apparent molal volumes of KSCN, NaClO_4 , and KI in aqueous solution have been calculated from densities and extrapolated to infinite dilution versus $m^{1/2}$. (Ideally the Redlich equation⁽¹⁷⁾ should have been used for this extrapolation, but it is easier to illustrate complex formation by the simpler apparent molal volume versus $m^{1/2}$ plot). Independent of extrapolation procedure, the partial molal volumes at infinite dilution, (with the exception of KSCN), agree well with literature values as shown in Table II. The values of Halasey⁽¹⁸⁾ are 5.1 $\text{cm}^3\text{-mol}^{-1}$ less than those reported here both at 15 and 25°C. We have reason to believe, however, that our values are the correct ones.⁽¹⁹⁾

The partial molal volumes of α - and β -cyclodextrin in water have also been determined. The values at infinite dilution are 601 ± 2 and $709 \pm 2 \text{ cm}^3\text{-mol}^{-1}$, respectively at 25°C . The agreement with the data of Shahidi *et al.*⁽¹²⁾ is excellent.

When α -cyclodextrin is added to an aqueous solution of KSCN, NaClO_4 , or KI, the apparent molal volume of the salt decreases as illustrated in Fig. 2. β -cyclodextrin, on the other hand, does not seem to affect the apparent molal volumes to any significant extent. However, β -cyclodextrin is only slightly soluble in water, about $0.016 \text{ mol}\cdot\text{kg}^{-1}$.⁽¹¹⁾ It is only possible to obtain reliable apparent molal volumes at salt concentrations exceeding about $0.02 \text{ mol}\cdot\text{kg}^{-1}$. Under these circumstances by far the largest fraction of anions are uncomplexed and the volumetric contribution from the few complexed ions would not count unless ΔV° of this complex formation was large (greater than $10 \text{ cm}^3\text{-mol}^{-1}$).

In any case the apparent molal volumes of KSCN, NaClO_4 , and KI in cyclodextrin-water solutions include two contributions; one from complexed and another from uncomplexed anions. The two terms can be separated by starting with Young's rule:⁽²⁰⁾

$$V_\phi = \alpha V_\phi(\text{MX}) + (1 - \alpha) V_\phi(\text{MCDX}) \quad (5)$$

where $V_\phi(\text{MX})$ and $V_\phi(\text{MCDX})$ are the apparent molal volumes of the salt when the anion is uncomplexed and when it is complexed, respectively, and α is the fraction of anions in the uncomplexed state, the same quantity as in Eq. (3). Strictly, Young's rule only applies in very dilute solutions, but it can be corrected for the effects of finite concentrations.⁽⁹⁾ On this basis it is possible to evaluate $V_\phi(\text{MCDX})$ at each concentration and carry out the extrapolation to infinite dilution. The result is also plotted in Fig. 2. The ΔV° of complex formation is the difference between this value, $V_2^\circ(\text{MCDX})$, and the partial molal volume of the salt at infinite dilution in pure water, $V_2^\circ(\text{MX})$.

The ΔV° data from both methods of measurement are presented in Table II. The error in ΔV° for anion- α -cyclodextrin complex formation from density measurements is estimated to be $\pm 0.5 \text{ cm}^3\text{-mol}^{-1}$, while the corresponding data for anion- β -cyclodextrin complex formation may include an error as high as $\pm 3 \text{ cm}^3\text{-mol}^{-1}$ due to the low solubility of β -cyclodextrin in water. The error in ΔV° values from conductivity measurements is probably about $\pm 1 \text{ cm}^3\text{-mol}^{-1}$. On this basis ΔV° from the two methods of measurement are in excellent agreement.

Table II. Partial Molal Volumes of the Salts and Volume Changes for Complex Formation of the Corresponding Anions in Aqueous Solution at Infinite Dilution

	$T^{\circ}\text{C}$	V_2°		ΔV°			
		This Work	Lit.	α -cyclodextrin		β -cyclodextrin	
				Density	Cond.	Density ^c	Cond.
KSCN	15	47.76	42.66 ^a	-3.5			
	25	49.82	44.70 ^a	-4.2	-3.1	0	1.5
	35	51.60	-	-5.1	-	-	-
NaClO ₄	15	41.10	-	-1.6	-	-	-
	25	42.89	42.93 ^b	-1.9	-1.4	6.5	8.0
	35	45.08	-	-2.0	-	-	-
KI	15	43.81	43.93 ^b	-7.4	-	-	-
	25	45.27	45.21 ^b	-5.8	-7.0	0	1.1
	35	46.14	46.28 ^b	-5.2	-	-	-

^aRef. 18. ^bFrom the compilation of Millero, Ref. 28. ^c ΔV° from density measurements are less reliable for β -cyclodextrin due to its low solubility of approximately 0.016 *m*.

4. DISCUSSION

Structural work on cyclodextrins in the crystalline state shows that α -cyclodextrin contains two water molecules situated in the cavity at well defined sites.⁽²¹⁾ The conformation is distorted. One of the glucose units is rotated inwards, and the macrocyclic ring is somewhat collapsed presumably so that the cavity diameter can match the diameter of the water molecule. When water is replaced by other guest molecules in the cavity, α -cyclodextrin becomes symmetrical.⁽²²⁾ Such a conformational change obviously contributes to the ΔV° data included in Table II. Its magnitude cannot be measured explicitly, but it seems that going from a collapsed to a symmetrical state must involve a positive contribution to ΔV° . Thus it seems unlikely that the negative ΔV° values can be ascribed to conformational changes.

β -cyclodextrin contains 6.5 water molecules that are statistically distributed between eight possible binding sites.⁽²³⁾ Crystallographic data does not indicate any conformational changes as water is replaced by

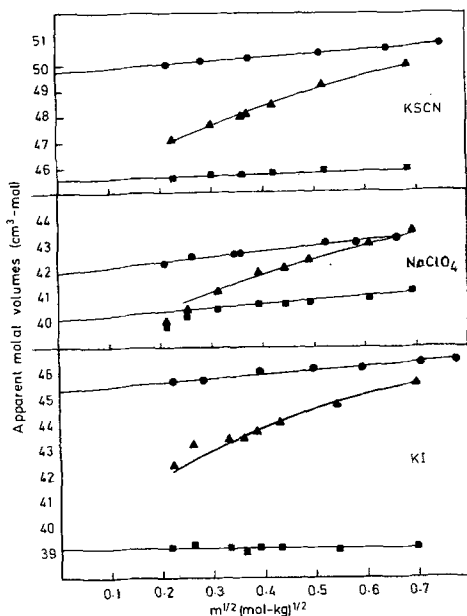


Fig. 2. Apparent molal volumes versus the square root of molality for: ● pure salt in aqueous solution, ▲ salt in water- β -cyclodextrin solutions, ■ salt where all anions have formed complexes with β -cyclodextrin (data after Young's rule have been applied to separate the various contributions).

other guests, but ultrasonic absorption data can be interpreted on the basis of conformational changes in both α - and β -cyclodextrin as complexes with other guests than water are formed.⁽⁸⁾ However, since different conformations of β -cyclodextrin cannot be detected crystallographically, their volumetric contribution must surely be small.

In the analogous case of cation-crown ether complex formation all ΔV° were positive; $10 \text{ cm}^3\text{-mol}^{-1}$ or larger for cations of a size compatible with the diameter of the crown ether cavity.⁽¹⁰⁾ Apparently the cations were dehydrated as they entered the crown ether cavity. Dehydration of the cations also appeared as the rate limiting factor in ultrasonic relaxation measurements.^(24,25) Similar ultrasonic measurements have been carried out for anion-cyclodextrin complex formation,⁽⁸⁾ and it shows that anion dehydration is not rate limiting. Further evidence that the anions are not dehydrated as they form complexes with cyclodextrins can be found in the work of Bergeron *et al.*⁽²⁶⁾ They studied complex formation between cyclodextrins and various carboxylates. Their conclusion is that the negatively charged carboxyl group must be

at least partially hydrated in the complexed state.

It appears that this can also be seen from ΔV° determinations. In the case of cation-crown ether complex formation where the cations do become dehydrated, ΔV is positive, about $10 \text{ cm}^3\text{-mol}^{-1}$ or more.⁽¹⁰⁾ In the case of anion-cyclodextrin complex formation where there appears to be no dehydration, ΔV° is negative.

So far the data suggest a simple model of complex formation between anions and cyclodextrins. In the case of α -cyclodextrin two water molecules contained in its cavity become replaced by a hydrated anion. The water molecules are added to bulk water increasing the total volume by 36 cm^3 for each mole of α -cyclodextrin. The hydrated anion, on the other hand, is removed from its normal aqueous surroundings decreasing the total volume by an amount equal to its partial molal volume. Since the partial molal volumes of the anions are known,⁽²⁷⁾ it is possible to test the model. The result is the following ΔV° data: -5, -10, and $-15 \text{ cm}^3\text{-mol}^{-1}$ for Γ , SCN^- , and ClO_4^- respectively, in opposite order to the observed values, but for Γ and SCN^- the values are in reasonable agreement with the experimental data considering the simple model used for the calculation. The ClO_4^- ionic radius is too large to fit into the cyclodextrin cavity, and it has been suggested that a straddle type complex is formed.⁽⁸⁾ Under such circumstances the hydrated ion will not be totally removed from its ordinary aqueous surroundings, and the measured ΔV° must be less negative than the value calculated from the model.

In the case of β -cyclodextrin as many as 6.5 water molecules could be replaced adding as much as 117 cm^3 for each mole of β -cyclodextrin to the total volume. The ΔV° for anion- β -cyclodextrin complex formation would then be at least one order of magnitude too large. This obvious discrepancy can be explained by: (a) the ideas underlying the proposed model are totally wrong, or (b) only a few of the water molecules originally situated in the β -cyclodextrin cavity become replaced as the hydrated anion forms its complex. The model as such is obviously too simple, but in a broad sense it covers the facts as derived from crystallographic data. On this basis it seems more likely that only a few of the 6.5 water molecules in the β -cyclodextrin cavity add to bulk water as the complexes form. The data suggest only about 3.

In conclusion all investigations so far support the idea that anions do not become dehydrated as they form complexes with the cyclodextrins. Since hydrated anions form complexes with cyclodextrins while cations apparently do not, it appears reasonable that the orient-

ation of the water molecules of the hydration sheeth play an important part in complex formation of this kind. Lastly, the more positive ΔV° values of anion- β -cyclodextrin complex formation compared to α -cyclodextrin can be explained simply by the fact that the β -cyclodextrin cavity contains more exchangeable water molecules.

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