Ultrasonic Investigations of Inclusion Complexation of α-Cyclodextrin by DMSO in Pseudo-Binary Aqueous System

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The paper reports the study of the complexation processes in aqueous solution of α-CD and DMSO. Cyclodextrins (CDs) (sometimes called cycloamyloses) are cyclic oligosaccharides formed by glucose units interconnected by α-(1,4) linkages; α-CD is one of three the most common CDs. It consists of six glucopyranose units. The speed of ultrasonic waves has been measured by the resonance method on Resoscan$^{\text{TM}}$ System apparatus. Some collateral data, such as density and heat capacity of the system, have also been measured. On the basis of the experimental data the excess adiabatic compressibility was determined. The extremes of the excess adiabatic compressibility function for different mixture compositions allowed us to establish the composition of molecular complexes formed in the solution. The obtained results suggest the formation of the α-CD with DMSO inclusion complexes with chemical stoichiometric ratio value of 1:1.

Keywords: ultrasonic speed, compressibility, complexation.

Notations

κ_S – adiabatic compressibility coefficient,
ρ – liquid density,
c – ultrasonic speed,
V_m – molar volume,
M – molecular weight,
x_2 – mole fraction,
T – temperature,
$K_{S,m}$ – adiabatic molar compressibility,
$K_{S,m}^E$ – excess molar adiabatic compressibility,
$K_{S,m}^{id}$ – ideal molar adiabatic compressibility,
$K_{S,i}^*$ – adiabatic molar compressibility for pure components,
$A_{p,i}^*$ – the product of the molar volume V_i^* and the isobaric expansivity $\alpha_{p,i}^*$,
$\alpha_{p,i}^*$ – isobaric expansivity for pure components,
$C_{p,i}^*$ – isobaric molar heat capacity.

1. Introduction

Cyclodextrins (CDs) have attracted a lot of interest over the years from research community, pharmaceutical companies, food industry and agriculture. Dextrins are very attractive components of artificial enzymes and other biomimetic materials and they are well-known compounds to form inclusion complexes with a variety of guests molecules. CDs are small cyclic maltoologisaccharides with six to nine glucose residues. Their molecules are often described as a torus. Cycloamyloses are aqueous soluble species; hydrogen bonding readily occurs between the hydroxyl groups projecting from ring and water. The interior may be filled with water molecules when they are present in the aqueous environment (NASCIMENTO *et al.*, 2004; DSOUZA, LIPKOWITZ, 1998; SZEJTLI, 1992; IMMEL, LICHTENTHALER, 1995; MIECZNIK, KACZMAREK, 2007). The structure of cyclodextrins provides a hydrophobic cavity that allows formation of inclusion complexes with a variety of non-polar organic molecules of an appropriated size. The driving forces leading to the inclusion complexation of cyclodextrins involve electrostatic interaction, van der Waals interaction, hydrophobic interaction, hydrogen bonding and release of conformational strain (LIU, GUO, 2002).

Mixtures of water with dimethyl sulfoxide (DMSO) are used as a solvent and a chemical reaction medium and play an interesting role in some biochemical processes. Studies of thermodynamic and transport properties of the DMSO and water system led to the accepted conclusion that in the mole fraction range of $x_{DMSO} = 0.3$ to 0.4 the DMSO-water interactions due to hydrogen bonds are at a maximum (Sikorska, Linde, 2008; Żwirbla *et al.*, 2005). However, there is still some disagreement of whether specific hydrogen bonded complexes are formed (Kaatze et al., 1989, 1990). Antioxidant properties of DMSO are used to remove excess acids from the body. DMSO is also often used as a drug carrier in conventional chemotherapy and in treatment of virus diseases due to its ability to easily penetrate infected cells. In case of cancer DMSO is especially useful in treatment of hard-to-reach tumors, e.g. within the brain (Last, 2013; Wang *et al.*, 2012). However, there is still a whole lot of debate going on about the possibility of using DMSO in clinical practice, its recommended doses and proper application. One method of carrying DMSO within the body is by complexes it may form with sugar, so the question arises whether α-CD is able to form inclusion complex with dimethyl sulfoxide.

2. Material and methods

The velocity of ultrasonic wave was measured by a resonance method (Lautscham *et al.*, 2000; Eggers, Kaatze, 1996) using a ResoScan^{TM} System (Germany) apparatus. The ultrasonic velocity is determined from a series of resonance frequencies of the resonator cell recorded during initialization. Then, only a single resonance peak (chosen automatically) is tracked, and from the changes of resonance frequency of this peak, the ultrasonic velocity is evaluated. Path length is fixed and equal to about 6 mm. ResoScan^{TM} System permits the measurements of the ultrasonic velocity with the accuracy of ± 0.01 m s^{-1} in two sample cells (0.200 ml capacity) in frequency range 7.3–8.4 MHz with temperature precision $\pm 0.05^\circ$C. Because of the high sensitivity from the multiple reflections of sound waves in resonators and because of the advantage of employing continuous wave signals, resonator techniques (sometimes named interferometers) are preferred for small volume sound velocity measurements.

The density was measured using a microprocessor gauge of the DMA 38 type by Anton Paar. This instrument permitted density measurements up to $3 \cdot 10^3$ kg·m^{-3} with an accuracy of $\pm 2 \cdot 10^{-1}$ kg·m^{-3}. The isobaric molar heat capacity was measured by using DSC Q2000 (TA Instruments) with temperature accuracy of ± 0.01 K and temperature precision accuracy of ± 0.01 K.

α-cyclodextrin (α-CD) (FLUKA, > 98%) and DMSO (FLUKA, > 99.9%) were used without further purification. Solutions were prepared by using first distilled, and then deionized water. The samples were prepared in two stages. Firstly, the initial aqueous solutions H$_2$O:α-CD at the ratio of 550:1 ($\sim$ 0.1 mol/l) and another one H$_2$O:DMSO at the same ratio, were made. Then, the two solutions were mixed in different compositions. Because the number of moles of H$_2$O was the same in both aqueous solutions, that is 550, and only the amount of remaining components was changed, it could be assumed that water was only the environment (surrounding) in which the interaction between α-CD and DMSO takes place. The influence of the environment was assumed to be "weak"; in the beginning water molecules remained in their initial structures but then they were modified during complexation process. Thus, the solution was in fact pseudo-binary and not ternary one. The concentration in mole fraction was defined as $x_2 = n_2/(n_1 + n_2)$ where x_2 was the mole fraction of DMSO, and n_1, n_2 were the number of moles of α-CD and DMSO, respectively; $x_2 = 0$ corresponds to a pure aqueous α-CD solution and $x_2 = 1$ to a pure aqueous DMSO solution. In all, 18 samples were prepared and the measurements were carried out in the temperature range 293.15–313.15 K in increments of 10 K. The maximal error of the solutions concentration, which includes solvent losses by evaporation during samples preparation, was estimated to be better than ± 0.0001 mole fraction.

3. Results and discussion

No matter what experimental method is used, the properties of the complexes can be determined only if their lifetime is longer than the time constant of the given method. Otherwise only average values are measured. In the first case, one determines the dependence of the given parameter on the concentration of the complexes in the solution while in the second case one studies the deviation from the additivity rule that is the excess quantities. The composition of molecular complexes formed in the solution due to the intermolecular forces is determined on the basis of the correlation between the deviation from reference system of some thermodynamic quantities and the composition of the mixture.

Very useful tool to study intermolecular forces, that are present in solutions and liquid mixtures, is ultrasonic method. This is achieved through evaluation of adiabatic compressibility of a system, κ_S, from precisely measured set of densities, ρ, together with the ultrasonic speeds, c, (at low frequency, for example 1 MHz) which are linked by the so-called Newton-Laplace equation

$$c = \sqrt{\frac{1}{\kappa_S \rho}}. \qquad (1)$$

Since the process of acoustic wave propagation in real systems is dissipative (thus irreversible) the compressibility determined from Eq. (1) is rather adiabatic than isentropic. The results of the ultrasonic velocity measurements are listed in Table 1 and presented in Fig. 1. The measured density values for the system studied are given in Table 1 and Fig. 2.

Table 1. Experimental results of density, ρ, ultrasonic velocity, c, heat capacity, $C_{p,m}$, and $\alpha^*_{p,i}$ in α-CD + H_2O + DMSO mixture at different compositions and temperatures. The values of adiabatic compressibility, k_S, molar adiabatic compressibility, $K_{S,m}$, excess function of adiabatic molar compressibility, $K^E_{S,m}$, and molar volume, V_m, were calculated according to the Eqs. (1), (2), (4), and (3), respectively.

X_2	ρ	c	k_s	$K_{s,m}$	$K^E_{s,m}$	V_m	$C_{p,m}$	$\alpha^*_{p,i}$
	10^{-3} kg·m^{-3}	[m·s^{-1}]	10^{-10} kgm^{-5}s^{-2}	10^{-6} m^{3}mol^{-1}Pa^{-1}	m^{3}mol^{-1}Pa^{-1}	m^{3}mol^{-1}	J·mol^{-1}·K^{-1}	10^{-4} K^{-1}
293.15 K								
0	1.0312	1500.260	4.3084	8.253	0	19.1553	99.19	3.075
0.05073	1.0279	1500.053	4.3235	8.274	−0.429	19.1366		
0.09852	1.0276	1501.013	4.3192	8.235	−0.787	19.0667		
0.1976	1.0245	1500.894	4.3330	8.219	−1.393	18.9674		
0.2559	1.0225	1498.034	4.3581	8.242	−1.663	18.9119		
0.3297	1.0207	1497.473	4.3690	8.223	−1.917	18.8279		
0.4021	1.0184	1495.847	4.3884	8.230	−2.071	18.7549		
0.4523	1.0168	1494.387	4.4039	8.237	−2.124	18.7042		
0.5048	1.0144	1500.987	4.3756	8.167	−2.133	18.6644		
0.5543	1.0136	1492.889	4.4267	8.234	−2.099	18.5999		
0.6002	1.0120	1492.325	4.4370	8.233	−2.030	18.5556		
0.6355	1.0111	1493.864	4.4318	8.206	−1.953	18.5155		
0.6695	1.0100	1491.738	4.4493	8.222	−1.860	18.4810		
0.7244	1.0084	1490.795	4.4620	8.220	−1.669	18.4214		
0.7891	1.0061	1489.995	4.4770	8.220	−1.384	18.3596		
0.897	1.0028	1488.072	4.5034	8.217	−0.761	18.2453		
0.9503	1.0014	1487.665	4.5121	8.205	−0.387	18.1843		
1	0.9995	1486.847	4.5257	8.209	0	18.1382	108.77	2.883
303.15 K								
0	1.0282	1525.053	4.1817	8.034	0	19.2112	113.08	3.084
0.05073	1.025	1524.685	4.1968	8.054	−0.977	19.1907		
0.09852	1.0256	1525.66	4.1889	8.002	−1.776	19.1039		
0.1976	1.0218	1525.241	4.2069	8.000	−3.080	19.0175		
0.2559	1.0198	1523.109	4.2270	8.015	−3.636	18.9619		
0.3297	1.0178	1522.584	4.2381	8.002	−4.132	18.8815		
0.4021	1.0157	1520.981	4.2559	8.003	−4.406	18.8047		
0.4523	1.0141	1519.598	4.2703	8.008	−4.477	18.7540		
0.5048	1.0118	1524.807	4.2509	7.954	−4.454	18.7124		
0.5543	1.0107	1518.238	4.2924	8.006	−4.344	18.6532		
0.6002	1.0092	1517.678	4.3019	8.004	−4.169	18.6071		
0.6355	1.0084	1518.863	4.2986	7.980	−3.987	18.5650		
0.6695	1.0072	1517.198	4.3132	7.993	−3.776	18.5323		
0.7244	1.0058	1516.335	4.3241	7.986	−3.357	18.4690		
0.7891	1.0035	1515.625	4.3381	7.985	−2.755	18.4071		
0.897	1.0002	1513.879	4.3625	7.980	−1.489	18.2927		
0.9503	0.9989	1513.587	4.3698	7.9661	−0.752	18.2298		
1	0.9969	1512.787	4.3832	7.971	0	18.1855	148.25	2.194

Table 1. [Cont.]

X_2	ρ	c	k_s	$K_{s,m}$	$K_{s,m}^E$	V_m	$C_{p,m}$	$\alpha_{p,i}^*$
	10^{-3} kg·m^{-3}	[m·s^{-1}]	10^{-10} kgm^{-5}s^{-2}	10^{-6} m^{3}mol^{-1}Pa^{-1}	m^{3}mol^{-1}Pa^{-1}	m^{3}mol^{-1}	J·mol^{-1}·K^{-1}	10^{-4} K^{-1}
313.15 K								
0	1.0248	1542.842	4.0994	7.902	0	19.2749	133.72	3.094
0.05073	1.0218	1542.565	4.1129	7.918	−1.842	19.2509		
0.09852	1.0216	1543.553	4.1084	7.879	−3.298	19.1787		
0.1976	1.0182	1541.898	4.1310	7.884	−5.555	19.0847		
0.2559	1.0163	1541.191	4.1425	7.882	−6.456	19.0272		
0.3297	1.0143	1540.71	4.1533	7.869	−7.198	18.9467		
0.4021	1.0123	1539.259	4.1693	7.867	−7.541	18.8679		
0.4523	1.0107	1537.928	4.1832	7.872	−7.575	18.8171		
0.5048	1.0084	1542.126	4.1700	7.829	−7.449	18.7755		
0.5543	1.0074	1536.702	4.2036	7.867	−7.189	18.7143		
0.6002	1.006	1536.162	4.2124	7.863	−6.834	18.6663		
0.6355	1.005	1536.146	4.2167	7.855	−6.490	18.6278		
0.6695	1.004	1535.725	4.2232	7.852	−6.104	18.5914		
0.7244	1.0025	1534.995	4.2335	7.844	−5.371	18.5298		
0.7891	1	1534.295	4.2480	7.847	−4.356	18.4716		
0.897	0.9967	1532.767	4.2705	7.839	−2.312	18.3569		
0.9503	0.9954	1532.426	4.2780	7.826	−1.157	18.2939		
1	0.9937	1534.75	4.2724	7.795	0	18.2440	219.92	2.899
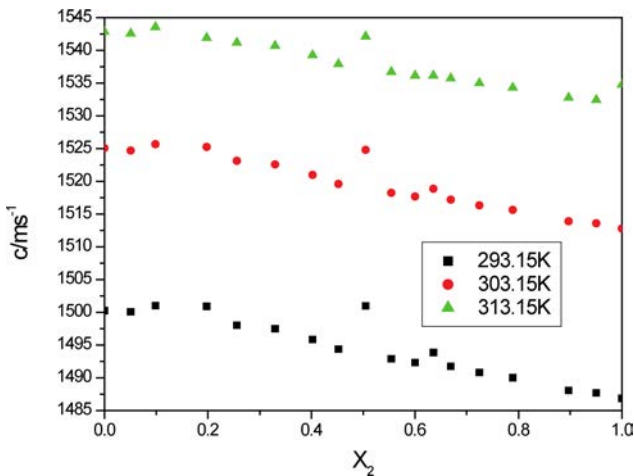
Fig. 1. Concentration dependence of the ultrasonic speed in the α-CD + H$_2$O + DMSO.
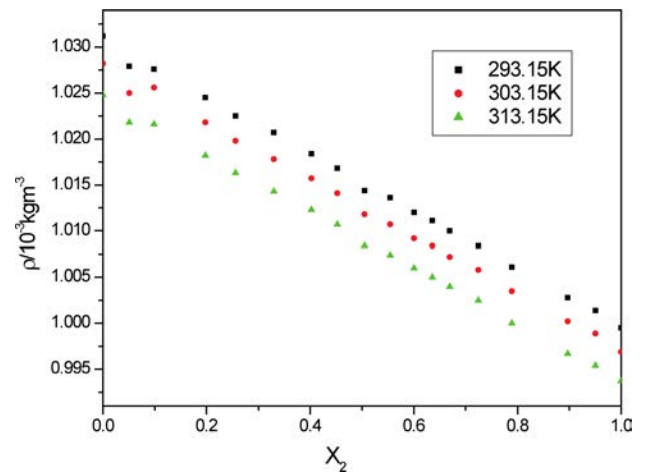
Fig. 2. Concentration dependence of density in the system α-CD + H$_2$O + DMSO.

Adiabatic compressibility, κ_S, can be transformed into its molar counterpart via the relation

$$K_{S,m} = V_m \kappa_S = -\left(\frac{\partial V_m}{\partial p}\right)_S, \qquad (2)$$

where V_m is the molar volume. Since the right hand side in the above equation is a second derivative of the molar Gibbs energy, its values are particularly sensitive to any change in the solution composition. Taking into account the way of the solutions preparation,

the molar volume, V_m, was calculated from the relation:

$$V_m = \frac{(1 - x_2)M_{\alpha-\text{CD}} + x_2 M_{\text{DMSO}} + 550 M_{\text{H}_2\text{O}}}{551\rho}, \quad (3)$$

where M_i is the molar mass of the i-th component. Excess function of adiabatic molar compressibility of the solutions expresses its deviation from the ideal (with no interaction between molecules) mixtures and is defined as

$$K_{S,m}^E = K_{s,m} - K_{S,m}^{id}. \qquad (4)$$

Table 2. Values of the coefficients, a_i, of the Redlich-Kister function (Eq. (9)) and their standard deviations σ for α-CD + H$_2$O + DMSO.

T/K	a_1/m$^3\cdot$mol$^{-1}\cdot$Pa^{-1}	a_2/ m$^3\cdot$mol$^{-1}\cdot$Pa^{-1}	a_3/ m$^3\cdot$mol$^{-1}\cdot$Pa^{-1}	$x_{2\,\min}$/(mol. frac.)
293.15	-8.53824 ± 0.00002	-0.39343 ± 0.00004	-0.01814 ± 0.0001	0.489
303.15	-17.84186 ± 0.00105	-2.41499 ± 0.00229	-0.32718 ± 0.00523	0.467
313.15	-29.86861 ± 0.01079	-7.4218 ± 0.0236	-1.84252 ± 0.05397	0.438

However, some thermodynamic parameters such as adiabatic compressibility do not obey so-called ideal mixing law

$$K_S^{id} \neq \sum x_i K_{S,i}^*, \qquad (5)$$

so the ideal adiabatic compressibility must be evaluated from the well-known thermodynamic identity:

$$K_S = K_T - T\frac{V\alpha_p^2}{C_p}, \qquad (6)$$

where K_T is the isothermal compressibility, α_p – the isobaric expansibility, and C_p – the heat capacity at constant pressure. Assuming the ideal mixing rules for all the variables present in the Eq. (6), except adiabatic compressibility, one arrives to the following formula for the molar adiabatic compressibility of an ideal mixture (DOUHÉRET et al., 2005):

$$K_{S,m}^{id} = \sum_i x_i K_{S,i}^*$$
$$-T\left[\frac{\sum_i x_i (A_{p,i}^*)^2}{\sum_i x_i C_{p,i}^*} - \sum_i x_i \frac{(A_{p,i}^*)^2}{C_{p,i}^*}\right], \quad (7)$$

where $A_{p,i}^*$ is the product of the molar volume $V_{m,i}$ and the isobaric expansivity $\alpha_{p,i}^*$, $C_{p,i}^*$ is the isobaric molar heat capacity, $K_{S,i}^*$ is the product of the molar volume V_i and the adiabatic compressibility $\kappa_{S,i}^*$ referred to "pure" i-th liquid component. In our case the "pure" components are the initial solutions, e.g. for $x_2 = 0$ and $x_2 = 1$. The values of isobaric expansivity for pure components, $\alpha_{p,i}^*$, were calculated from density measurement data using the relation

$$\alpha_p = -\frac{1}{T}\left(\frac{\partial V}{\partial T}\right)_p. \qquad (8)$$

Table 1 contains the experimental values needed to calculate ideal molar compressibility of the reference system.

When analyzing the dependence of density on the system composition (Fig. 2), nearly linear behaviour is observed for the system (α-CD + H$_2$O + DMSO). The curves for different temperatures are parallel and there is no maximum/minimum whatsoever. Effect of temperature on the processes occurring in the system is the same as in the initial solution. In contrast, the dependence of ultrasonic speed on the system composition is strongly non-linear (Fig. 1). KAWAIZUMI *et al.*

(1997) explain the appearance of a maximum in the ultrasonic speed with the formation of free complexes in the solution, and the position of maximum velocity indicates the type and composition of the complexes.

The values of $K_{S,m}^E$ were calculated according to the Eqs. (4) and (7), and their dependence upon composition was fitted to Redlich-Kister polynomial,

$$K_{S,m}^E = x_2(1 - x_2)\sum_{i=1}^{3} a_i(1 - 2x_2)^{i-1}. \qquad (9)$$

The values of the parameters a_i and their standard deviations σ_i were determined using the least-square procedure employing Marquardt's algorithm with all data points weighted equally, and are listed in Table 2. The results of the fit shown in Fig. 3 reveal that $K_{S,m}^E < 0$ over the whole mole fraction and temperature range. Because the measured values of $K_{s,m}$ are smaller than those of the ideal ones, the new solution structure is more packed and rigid. The observed minimum depends on temperature and DMSO concentration (Table 2) and shifts from $x_{2,\min} = 0.489$ at $T = 288.15$ K to $x_{2,\min} = 0.438$ at $T = 313.15$ K.
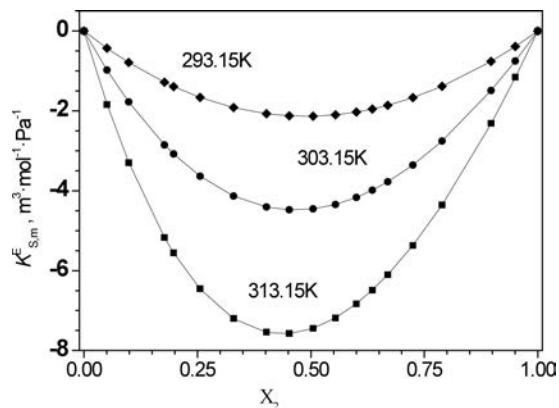
Fig. 3. Concentration dependence of excess function of adiabatic molar compressibility in the system α-CD + H$_2$O + DMSO. Solid lines represents the fit of Redlich-Kister function given by Eq. (9) to the calculated excess function of molar compressibility.

4. Conclusions

The ultrasonic investigation of formation of the inclusion complexes in aqueous solution of α-cyclodextrin and DMSO leads to the following conclusions:

1. In aqueous solution of α-cyclodextrin and DMSO supramolecular structures are formed. The driving force standing behind the formation of inclusion complexes could be pushing out of the polar molecules from the hydrophobic gap which leads to the state of lower energy (SZEJTLI, 1998). The strength of chemical bond depends on the matching of guest and host to one another and can change with temperature. The formation of complexes does not involve the formation nor breaking of covalent bonds. The new stable structure of particular composition is formed.

2. In the system studied a strong molecular interaction occurs between the host and the guest molecules, which is indicated by the local maximum of the ultrasound velocity. The position of the maximum velocity depends on the temperature and shifts from $x_{2,\min} = 0.489$ mole fraction of DMSO at $T = 293.15$ K to $x_{2,\min} = 0.438$ mole fraction of DMSO at $T = 313.15$ K. This is confirmed by the negative values of the excess adiabatic compressibility across the entire composition and temperature ranges, which means that the deviation from ideality is in the direction of greater resistance to compression (i.e. enhanced rigidity).

3. The position of the velocity maximum at $x_2 = 0.5$ mole fraction of DMSO corresponds to the minimum of the excess compressibility. Although the position of the minimum of excess compressibility changes slightly with temperature, its value remains close to 0.5 mole fraction of DMSO which suggests the formation of the molecular complexes with stoichiometric ratio of 1:1. The factor determining the ability of cyclodextrin to make complexes is the size of the interior cavity of the torus which depends on the number of glucopyranose units. Basing on theses parameters it was found that α-cyclodextrin can make complexes with aliphatic units and the compounds of small molar mass, like for example DMSO (REIJENGA *et al.*, 1997).

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