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ULTRASONIC INVESTIGATIONS OF INCLUSION COMPLEXES OF CYCLODEXTRINS WITH AMPHIPHILIC SUBSTANCES – FURTHER RESULTS AND CONCLUSIONS

A. BALCERZAK

Institute of Fundamental Technological Research
Polish Academy of Sciences
Świętokrzyska 21, 00-049 Warszawa, Poland
email: abalcerz@ippt.gov.pl

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On the basis of formerly made and published [1–3] ultrasonic measurements of aqueous solutions of α- or β-cyclodextrin with amphiphilic substances, calculations have been done and new conclusions drawn. These calculations and conclusions explain some experimental results concerning the stability of inclusion complexes of cyclodextrin with amphiphilic substances and the mechanism of the formation of such complexes.

Key words: ultrasonic relaxation, cyclodextrins, amphiphilic substances, inclusion complexes, complexation mechanism.

1. Introduction

The results of ultrasonic absorption and speed of sound measurements for aqueous solutions of α-cyclodextrin (αCD) or β-cyclodextrin (βCD) with organic ions formed by the dissociation of amphiphilic substances (AS) were presented in earlier papers [1–3]. One or two ultrasonic relaxation processes were established for all the investigated systems. Thermodynamic and kinetic parameters related to those processes were calculated. Further conclusions derived from the results obtained are presented in this work.

2. Discussion of the results obtained from ultrasonic investigations

In [1–3] a low-frequency relaxation process has been established for octyl and longer hydrocarbon chains of AS in βCD aqueous solutions, whereas in the αCD solutions this process has been observed beginning from a decyl chain. Furthermore, the absolute value of the free enthalpy change, ΔG^0, connected with this relaxation process is larger for the system with βCD than for that with αCD. This fact evidences a higher stability

of the complex of AS with βCD than of that with αCD. Table 1 presents the values of the free enthalpy changes, ΔG^0, for examples of aqueous solutions of αCD or βCD with sodium alkyl sulfates.

Table 1. Comparison of free enthalpy changes, ΔG^0, for aqueous solutions of sodium alkyl sulfates with α- or β-cyclodextrin [1, 2].

name of sodium alkyl sulfate	ΔG^0 [kJ/mol]	
	αCD	βCD
sodium octyl sulfate	–	-8.60
sodium decyl sulfate	-8.45	-9.18
sodium dodecyl sulfate	-10.0	-10.6
sodium tetradecyl sulfate	-11.4	-11.8

As a result of smaller steric hindrances, the larger cavity of βCD than that of αCD enables a deeper penetration of the alkyl chain. In many works, a correspondence of the dimension of the cavity and the penetrating moiety has been pointed out as the decisive factor. This is the so called geometric factor. The deeper penetration causes a higher stability of the CD-AS inclusion complex. Simple geometric considerations are able to explain this feature. The volumes of the αCD and βCD cavities are equal to 95–110 Å^3 and 270 Å^3, respectively [4]. The length, L, and the volume, V_L, of the fully unfolded alkyl chain C_nH_{2n+1} can be expressed as:

$$L = 1.5 + 1.265(n-1), \tag{1}$$

$$V_L = 27.4 + 26.9(n-1). \tag{2}$$

Each chain kink shortens the chain by 1.25 Å and increases its volume by 20–50 Å^3. Thus, the αCD cavity can accommodate four or three, with one chain kink, methylene groups. On the other hand, the βCD cavity can contain also four methylene groups of the straight chain, but it can contain even eight of those groups, when two kinks of the chain occur (there is enough space in the βCD cavity for two kinks). This results in a higher stability of the complexes with βCD than that with αCD.

The absolute values of isentropic molar volume change, $|\Delta V_S|$, accompanying the occurrence of the low-frequency ultrasonic relaxation process for some αCD-AS systems are presented in Table 2. They were determined by means of ultrasonic spectroscopy measurements [1]. The volume of the methylene group is 26.9 Å^3, which corresponds 16.2 cm^3/mol. In the third column of Table 2, the calculated ratio, E, of $|\Delta V_S|$ and one mole of the methylene group is given.

From data presented in Table 2, one can conclude that a deeper penetration (E increases) of the AS alkyl chain (which is built of methylene groups) into the CD cavity

with inceasing length of the alkyl chain increases. This observation is a direct evidence of the postulate mentioned in the references, where that postulate has been derived indirectly from the folowing facts: a) the hydrophobicity increases with increasing length of the alkyl chain, b) the stability of the CD-AS complexes is inceasing when the chain of AS becomes longer, and c) hydrophobic interactions play a fundamental role in the formation of the complex between CD and AS.

Table 2. Absolute values of the isentropic molar volume change ΔV_S[1] and the ratio E for the systems of α-cyclodextrin + amphiphilic substance.

amphiphilic substance	ΔV_S [cm^3/mol]	E
sodium decyl sulfate	6.9	0.43
sodium dodecyl sulfate	13.6	0.84
sodium tetradecyl sulfate	20.3	1.25

OKUBO *et al*. [5] carried out kinetic investigations of the complexation of CD with AS by the stopped-flow method based on conductivity measurements during the concentration jump of AS. They applied a simple scheme of the complexation reaction:

$$\mathrm{CD} + \mathrm{AS} \underset{k_{(-)}}{\overset{k}{\rightleftarrows}} \mathrm{CD} \bullet \mathrm{AS}, \tag{3}$$

where CD and AS, as previously, denote the cyclodextrin and the amphiphilic substance, respectively. The inclusion complex is CD • AS.

The values of the rate constant k of the direct reaction in Eq. (3) are contained in the range 10^2–$2 \cdot 10^3$ $\mathrm{M}^{-1}\mathrm{s}^{-1}$. From a comparison of the equilibrium constant of reaction (3), which is the ratio of the rate constant k of the direct reaction and the rate constant $k_{(-)}$ of the opposite reaction, with the association constants obtained by static methods for the complexes tested in [5] – (Table 3) one can draw a general conclusion that $k/k_{(-)} < K_A$. Thus, Eq. (3) does not reflect properly the complexation mechanism of CD with AS.

The results presented in [5] and [1–3] can be explained by the assumption of the following complexation mechanism for the system cyclodextrin + amphiphilic substance:

$$\mathrm{CD} + \mathrm{AS} \overset{K_D}{\longleftrightarrow} (\mathrm{CD} \bullet \mathrm{AS})' \overset{K_P}{\longleftrightarrow} (\mathrm{CD} \bullet \mathrm{AS})'' \overset{K_K}{\longleftrightarrow} \mathrm{CD} \bullet \mathrm{AS}, \tag{4}$$

where (CD•AS)$'$ and (CD•AS)$''$ denote intermediate forms of the inclusion complex of CD with AS, CD • AS is its final form. K_D, K_P and K_K are the equilibrium constants for the respective steps of reaction (4).

Generally, it can be expected that the first step of the complexation is a process controlled by diffusion [12, 13]. The rate constant of this process is expressed by Eq. (5):

$$k_D = 4\pi \left(D_{\mathrm{CD}} + D_{\mathrm{AS}}\right) R \cdot N \cdot 10^3, \tag{5}$$

Table 3. Values of the ratio of the rate constants $k/k_{(-)}$ and association constants K_A for some aqueous systems of cyclodextrin + amphiphilic substance. Temperature 25°C.

system	$k/k_{(-)}$, M^{-1} [5]	K_A, M^{-1}
α CD + sodium dodecyl sulfate	160	2480 [6], 1120 [7], 754 [8], 1410 [9], 21000 [4]
α CD + sodium hexanesulfonate	95	450 [6], 379 [7]
α CD + sodium heptanesulfonate	100	676 [7]
α CD + sodium octanesulfonate	115	1080 [7]
α CD + sodium decanesulfonate	130	2020 [7]
α CD + sodium dodecanesulfonate	135	2140 [7]
β CD + sodium decanesulfonate	180	4090 [10], 5360 [11]

where N is the Avogadro number, D_{CD} and D_{AS} denote the diffusion coefficients for cyclodextrin and the organic ion originating from the amphiphilic substance, respectively. R is the distance between the ion and the cyclodextrin molecule when the complex is created. The factor 10^3 results from the concentration unit: mole·dm^{-3}. Typical values of the diffusion coefficient for the organic ions, D_{AS}, equal $5.9 \cdot 10^{-10}\mathrm{m}^2\mathrm{s}^{-1}$ and $5 \cdot 10^{-10}\mathrm{m}^2\mathrm{s}^{-1}$ for the dodecyl sulfate anion [14] and the dodecyltrimethylammonium cation [15], respectively. The values of the diffusion coefficient cited in literature for αCD and βCD are $3.4 \cdot 10^{-10}\mathrm{m}^2\mathrm{s}^{-1}$ [16] and $3.2 \cdot 10^{-10}\mathrm{m}^2\mathrm{s}^{-1}$ [17, 18], respectively. It can be assumed that R equals the radius of the αCD or βCD molecules, i.e. 8–10 10^{-10}m. Then k_D is a number from the range 5–7 $\cdot 10^9$ $\mathrm{M}^{-1}\mathrm{s}^{-1}$. The investigation of a reactions with such a rate constant is possible by means of ultrasonic spectroscopy. However, it should be stressed that the appearance of the ultrasonic relaxation process depends also on: a) the existence of well-separated energy barriers, b) the occurrence of each form of the molecular system during relaxation in sufficient concentrations at the equilibrium state, and c) a distinct isentropic change of volume connected with the investigated kinetic step [19]. Generally, the formation (association) constants of the cyclodextrin inclusion complexes with AS have high values, but are sometimes very different, (Table 3). This is an evidence of the total shift of the equilibrium toward the product, i.e. toward the inclusion complex. Thus, at equilibrium, the concentrations of the substrates are very low. Therefore the first step of the complexation reaction, Eq. (4), can not be detected by ultrasonic measurements since condition b) is not fulfilled.

In fact, the stopped-flow method applied in [5] allows investigating the second step of the proposed complexation mechanism (Eq. (4)). The rate constants obtained in this work refer to that step. This method cannot detect the first step because this step is too fast (see the calculated value of the rate constant k_D). The forward rate constant of this step, k_p, can be written as [20, 21]:

$$k_p = \frac{k}{K_D}. \tag{6}$$

According to the statement that the low-frequency ultrasonic relaxation process detected and investigated in [1–3], and connected with the occurrence of the inclusion complex, is caused by a fast first-order or pseudo-first-order reaction, a third step in the model of the complexation mechanism should be added. This is the last step in Eq. (4).

The model of the complexation mechanism described above is similar to that proposed for the mechanism of the complex formation by crown ethers, i.e. the Eigen-Winkler mechanism [19, 22, 23]. This model, initially in a simpler two-step version, was also applied in the investigation of the complex formation of a macrocyclic antibiotic – valinomycin. The possibility of the existence of a three-step mechanism in the case of formation of cyclodextrin inclusion complexes was mentioned by HALL *et al.* [13]. This kind of mechanism was also postulated for the complexation reaction of βCD with the 2-(p-toluidinyl)naphthalene-6-sulfonate ion [24].

It seems that the following description of the complexation mechanism for the cyclodextrin and the amphiphilic substance can be proposed. (CD • AS)$'$ is formed after meeting the hydrated molecule of CD with the hydrated organic ion from the dissociated AS. This is the fast step and the rate constant of the direct reaction is close to k_D. The form (CD • AS)$''$ is produced from the previous one after a partial dehydration of AS and CD with an expulsion of water molecules from the CD cavity by the hydrophobic hydrocarbon chain of AS. The equilibrium constant K_p equals the ratio of the rate constants $k_p/k_{(-)}$. CD•AS is created from (CD•S)$''$ when the alkyl chain of AS penetrates deeply the CD cavity and the stable complex of CD with AS is formed. This complex is stabilised mainly by hydrophobic interactions between the AS chain and the CD cavity. The equilibrium constant of this step, K_K, equals the constant K for the low-frequency ultrasonic process; K has been calculated in [1, 3].

3. Conclusions

Applying geometric considerations to the cyclodextrin cavity and the alkyl chain of the amphiphilic substance, the following experimental facts can be explained: a) the higher stability of β-cyclodextrin complexes with amphiphilic substances in comparison with the corresponding complexes of α-cyclodextrin and b) the increasing stability of these complexes when the hydrocarbon chain of the amphiphilic substance becomes longer. A three-step mechanism of the inclusion complex formation has been proposed as a conclusion drawn from the referred chemical kinetic and the ultrasonic investigations performed in our laboratory.

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