

Thermogravimetric Properties of Inclusion Complexes of β -Cyclodextrin with Benzene, Acetylsalicylic Acid and Methyl Salicylate

A. SZAFRANEK

Institute of Physics, University of Gdańsk, 80–952 Gdańsk, ul. Wita Stwosza 57, Poland.

and

J. SZAFRANEK

Department of Chemistry, University of Gdańsk, 80–952 Gdańsk, ul. Sobieskiego 18, Poland.

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Abstract. This paper reports TG analyses of inclusion complexes of β -cyclodextrin with benzene, acetylsalicylic acid and methyl salicylate. The data were used for calculation of the compositions of the three body complexes and the apparent kinetic parameters of the thermal decompositions. Water exclusion proceeds as a reaction with order $n = 1$ and an activation energy about 20 kJ/mol. The expulsion of aromatic guest molecules follows an $n = 1$ order process with the activation energy above 155 kJ/mol, except that for the methyl salicylate complex, which was found to be ca. 64 kJ/mol.

Key words: β -Cyclodextrin, inclusion complexes, aromatic complexes, thermogravimetry.

1. Introduction

β -Cyclodextrin is a toroidal molecule composed of seven (1 \rightarrow 4) linked α -D-glucopyranosyl residues. The molecule is a truncated cone with primary and secondary hydroxyl groups crowning the narrower and the wider rims. Methine protons and glucosidic oxygen atoms are oriented into the interior of the cavity. The cavity is capable of including various guest molecules to form noncovalently bonded inclusion complexes, i.e. to trap the external molecules (guest molecules) inside the hole in the solid state and in aqueous solutions [1].

Considerable effort has been devoted to determining the mechanism of the inclusion complex formation process. It is a general belief that the driving force for complex formation is the removal of high-energy water molecules by guest molecules from the cavity, and London dispersion intermolecular interactions [2–4].

The inclusion phenomenon has been extensively applied in the pharmaceutical field because of its ability to improve aqueous solubility, dissolution and release rates, bioavailability, chemical stability, physical stability and modification of the pharmacokinetics of various drug molecules [5].

The objective of the present paper is to examine the thermal decomposition of the

β -cyclodextrin complexes with simple aromatic compounds, some of them being pharmaceutical agents. The compositions and their changes during programmeable heatings of the complexes in the solid phase were studied.

2. Experimental

β -Cyclodextrin (Aldrich, U.S.A.) and acetylsalicylic acid (POCh, Poland) were recrystallized from glass-distilled water. Benzene and methyl salicylate (POCh, Poland) were distilled. For preparation of the solid complexes, the method of precipitation was used following the literature procedures [6]. Thus, the complexes were prepared by dissolving β -cyclodextrin (1.135 g, 0.001 mol) in 100 mL of water and adding appropriate amounts of the aromatic compound giving a molecular ratio of 1 : 1 (benzene 0.078 g, acetylsalicylic acid 0.180 g, methyl salicylate 0.152 g). The samples were left for 24 h at room temperature with occasional shaking and the precipitates were then filtered, washed and dried at ambient temperature providing 0.92 g of benzene, 0.78 g of acetylsalicylic acid and 0.54 g of the methyl salicylate complex. The complexes were then subject to thermogravimetric studies.

A derivatograph (MOM, Budapest, Hungary) was used for the thermal decomposition studies, in which 50 mg samples (measured at a scale 0–100 divisions with ± 0.25 mg accuracy) were run against a standard of 50 mg α -Al₂O₃. A platinum semimicro crucible was used for the thermogravimetry. Linear temperature programming of *ca.* 5°C/min was used. A basic sensitivity of 10⁻¹⁰ A/mm/m was reduced to 1/10 for DTG and 1/3 for DTA curves.

Thermogravimetric–mass spectrometry measurements were carried out under high vacuum using a Varian MAT 711 mass spectrometer equipped with a temperature programmeable direct probe inserted into the ion source.

The linear regression method was employed for calculations.

3. Results and Discussion

To preclude the possibility that the complexes obtained are simply physical mixtures, the thermogravimetric (TG) curves of the products and component mixtures were recorded. When guest molecules are incorporated in the molecular cavity, the thermal properties are modified and one of the best methods for detecting formation complexes is the TG method [8].

The preparation method employed did not entirely exclude simultaneous crystallization of the CD–water complex [7]. Nevertheless, this could not change the apparent kinetic parameters of guest expulsion processes calculated from TG curves, which were the aim of the studies, but only the compositions of the complexes.

Thermal analysis curves of the β -cyclodextrin–acetylsalicylic acid complex are shown in Figure 1 for a heating rate of 5°C/min. The low-temperature peaks at 67°C and 88°C in the DTG curve correspond to the loss of water molecules,

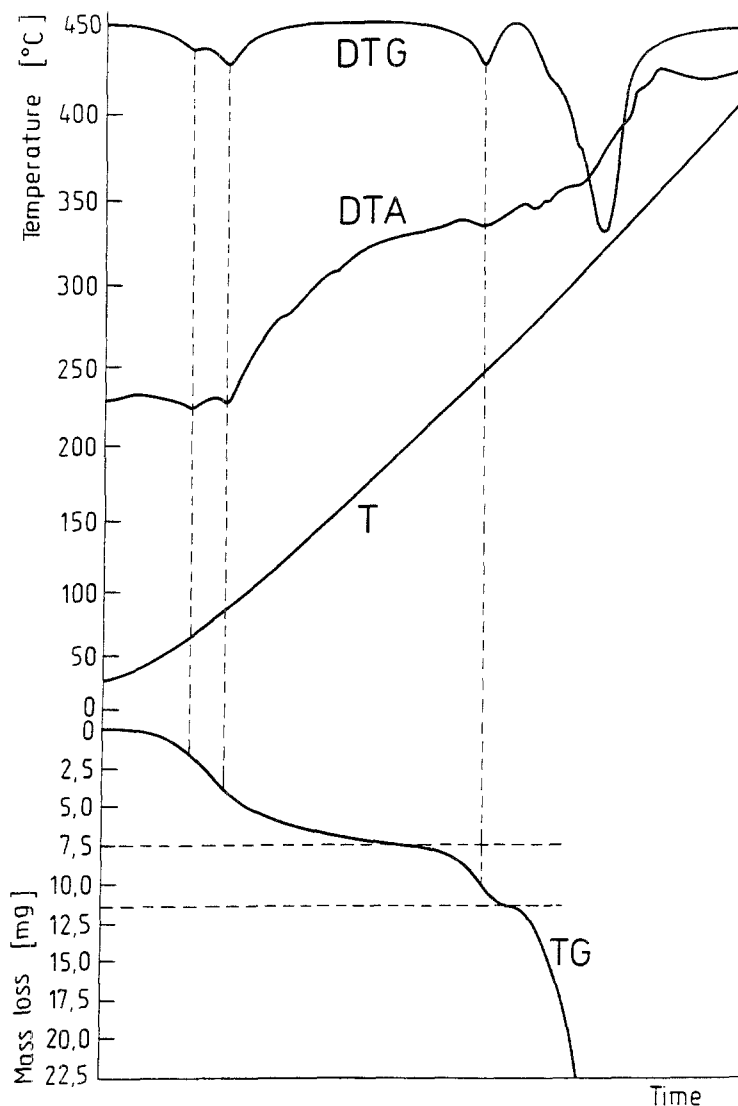


Fig. 1. Thermal curves of the hydrate of the β -cyclodextrin-acetylsalicylic acid complex. Average heating rate $\Phi = 5^\circ\text{C}/\text{min}$.

which escape in two steps from the complex in spite of a single stage process observed for the β -cyclodextrin hydrate alone (Figure 2) [9]. Dehydrations occur as endothermic processes with negative peaks in the DTA curve. The total loss of weight in the temperature range 40–190°C (7.5 mg per 50 mg sample) suggests 12.2 water molecules (Table 1) in the β -CD-acetylsalicylic acid complex, almost the same as in β -cyclodextrin hydrate [10].

The thermogravimetric parameters of the water exclusion processes of the com-

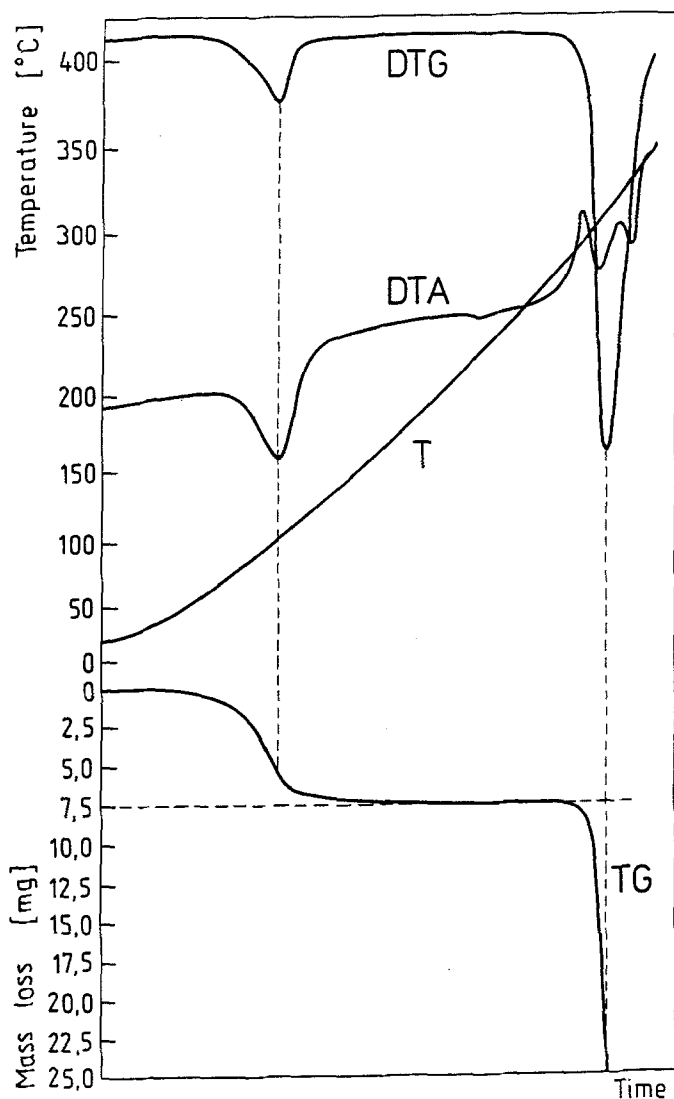


Fig. 2. Thermal curves of the β -cyclodextrin-water complex. Average heating rate $\Phi = 5^\circ\text{C}/\text{min}$.

plexes studied are included in Table I. All the complexes studied show peaks in the DTG and DTA curves, which could be assigned to expulsion of water molecules. The water content was found to be 8 to 12 molecules per complex. The greater the water content in the complex, the more complex is the DTA curve. Thus, thermogravimetric curves in the water expulsion range alone supply evidence for formation of the complexes.

On heating the complexes above the water expulsion range, peaks related to

TABLE I. Thermogravimetric properties of the complexes in the temperature range of water exclusion.

Complex with	No. of water molecules	Temperature of water loss °C	Maximum of DTG °C	Maximum of DTA °C
water	11.1 ± 0.5	40 – 140	100	100
benzene	11.5 ± 0.8	40 – 180	72	55
			127	114
				128
acetylsalicylic acid	12.2 ± 0.8	40 – 187	67	67
			88	88
				127
methyl salicylate	8.0 ± 2	40 – 160	–	153
				113
				142

TABLE II. Thermogravimetric properties of the complexes in the temperature range above water expulsion.

Complex with	No of guest molecules	Temperature range °C	Guest expulsion		β -CD decomp.
			Max. DTG °C	Max. DTA °C	Max. DTG °C
water	11.1 ± 0.5	40 – 170	100	100	312
benzene	0.4 ± 0.1*	224 – 268	259	259	295
acetylsalicylic acid	0.6 ± 0.1*	215 – 260	245	245	322
methyl salicylate	1.0 ± 0.2*	170 – 290	284	284	313

* The compositions were checked by UV spectrophotometric analysis of the complex solutions.

structural changes (without weight loss), expulsion of guest molecules and finally thermal decomposition of β -cyclodextrin alone (Figure 2, Table II) can be observed. The aromatic guests in the cavity were detected by mass spectrometry with a heated probe and monitoring the ion currents at m/z 78 (benzene), m/z 152 (methyl salicylate) and m/z 138 (acetylsalicylic acid). The last guest molecule appears to decompose with ketene elimination before leaving the cavity as no molecular ion was recorded with m/z 138.

The complexes of cyclodextrin break down at low temperature according to the scheme:



followed by a higher temperature process:



where CD represents cyclodextrin and X the included molecule.

The kinetics of both processes can be described by the expression:

$$\frac{\alpha}{t} = k(T) f(\alpha) \quad (3)$$

where: α is the fractional conversion,

$$k(T) = A \exp(-E/RT).$$

and A = frequency factor; E = activation energy; R = gas constant; and T = absolute temperature.

Assuming constant heating rates $\Phi = \frac{T}{t}$, and separating the variables, one obtains

$$\int_0^\alpha \frac{\alpha}{f(\alpha)} = \frac{A}{\Phi} \int_0^T e^{-E/RT} T \quad (4)$$

Coats and Redfern [11], applying the function,

$$f(\alpha) = (1 - \alpha)^n$$

derived for $n \neq 1$

$$\log \left[\frac{1 - (1 - \alpha)^{1-n}}{T^2(1 - n)} \right] = \log \frac{AR}{\Phi E} \left[1 - \frac{2RT}{E} \right] - \frac{E}{2.3RT} \quad (5)$$

and for $n = 1$

$$\log \left[\frac{-\log(1 - \alpha)}{T^2} \right] = \log \frac{AR}{\Phi E} \left[1 - \frac{2RT}{E} \right] - \frac{E}{2.3RT} \quad (6)$$

When $E \gg 2RT$, calculation of the activation energy E and the frequency factor A is possible as an appropriately chosen value for n will give a straight-line relation [11] for the experimental points of the TG curve.

The calculated parameters of water exclusion are collated in Table III and those for loss of the guest molecule in Table IV. For calculations, n values between -0.5 and 1.5 were chosen, but the best correlation coefficients were obtained for $n = 1$ despite $n = 0$ having been reported earlier for the water complex [9].

TABLE III. Apparent kinetic parameters of thermal decomposition of inclusion complex hydrates of β -CD, (water expulsion range) calculated from Equations 5 and 6.

Complex with	E kJ/mol	n	$\log A$ s^{-1}	r
water	57.7 ± 1.0	0	5.52 ± 0.30	-0.9979
benzene	20.7 ± 0.4	1	-0.47 ± 0.04	-0.9957
acetylsalicylic acid	22.3 ± 1.6	1	-0.13 ± 0.01	-0.9923
methyl salicylate	19.7 ± 0.3	1	-0.47 ± 0.03	-0.9979

TABLE IV. Apparent kinetic parameters of the thermal decomposition of inclusion complex hydrates of β -CD, aromatic guest expulsion range.

Complex with	E kJ/mol	n	$\log A^*$ s^{-1}	r
water	57.7 ± 1.0	0	5.5 ± 0.3	-0.9979
benzene	171.0 ± 10.9	1	14.1 ± 1.2	-0.9896
acetylsalicylic acid	155.3 ± 4.4	1	13.1 ± 0.8	-0.9957
methyl salicylate	64.1 ± 1.8	1	3.3 ± 0.2	-0.9916

* Contributions of $2RT/E$ factors (Equation 6) in A values are in the range of the errors.

Activation energies of water expulsion from all three complexes studied were found to be significantly lower than that of the water complex [9]. The energies were computed for α values in the range 0.2 – 0.8 for the water expulsion process (average values, Table III), but those calculated for distinct stages of the processes were 21.8 ± 0.8 , and 16.1 ± 0.8 for the benzene and 48.9 ± 2.4 , 11.2 ± 0.6 and 6.6 ± 0.9 kJ/mol for the acetylsalicylic acid complex.

Aromatic guest molecule exclusion follows an $n = 1$ reaction with an activation energy (calculated for $\alpha = 0.1 - 0.9$) above 160 kJ/mol, except for methyl salicylate, where a value of only 64 kJ/mol was observed. These differences could be explained by the variation in mutual host–guest molecule positions, including the extent of the penetration into the cavity. The complex of methyl salicylate has the lowest water and the highest guest molecule content, suggesting that a guest molecule removes water molecules from the cavity during inclusion. E.g. for β -cyclodextrin hydrates, 6.13 water molecules occupy the cavity [10] but it decreases

to only three molecules for the ethanol complex [12].

A kinetic compensation effect between the E and A values is observed for the thermal decomposition of β -CD complexes (Table IV) similar to literature data [13]. A greater E value corresponds to a greater A value according to a linear relation

$$\log A = eE + B$$

where B and e are constants.

Understanding the nature of the inclusion process is an important problem for biophysics. Complex formation is accompanied by removal of high-energy water molecules by guest molecules from the cavity, conformational changes, hydrophobic interactions and London dispersion interactions [2–4]. Our thermogravimetric studies provided direct proof of such energetical changes of water molecule states in the complexes.

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