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Microcalorimetric and spectrographic studies on host–guest interactions of α-, β-, γ- and Mβ-cyclodextrin with resveratrol

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ABSTRACT

Thermal effects of inclusion processes of α-, β-, γ- and Mβ-cyclodextrin with resveratrol (RES) in aqueous solutions were determined by isothermal titration calorimetry (ITC) with nanowatt sensitivity at the temperature of 298.15 K. Standard enthalpy changes, stoichiometry and equilibrium constants of the inclusion complexes were derived from the direct calorimetric data utilizing nonlinear simulation. The thermodynamic parameters were discussed in the light of weak interactions between the host and the guest molecules combining with UV spectral message. The results indicate that all of the complexes formed in the aqueous solutions are in 1:1 stoichiometry. The binding processes of α-, β- and Mβ-cyclodextrin with the guest are mainly driven by enthalpy, while that of γ-cyclodextrin with the drug is driven by both enthalpy and entropy.

1. Introduction

Resveratrol (3,5,4′-trihydroxy-*trans*-stilbene), a polyphenol, has been found in a wide variety of about 70 plant species, including grapes, mulberries, and peanuts [1], which could protect against a range of illnesses and diseases, e.g., cardiovascular diseases [2–4], cancer [5,6], viral attacks [7], neurodegenerative diseases [8] and ageing [9]. Furthermore, it could increase lifespan [10] and physical activity of diverse species [11,12]. Various studies have also indicated that resveratrol shows several interesting biological effects such as antioxidant [13–15], anti-inflammatory [16] and anti-proliferative activities [17]. However, due to its low water solubility, resveratrol cannot be used for oral administration. This limitation could be overcome by the formation of inclusion complexes of the drug with cyclodextrins [18].

Cyclodextrins (CDs) are the most prominent host molecules used in supramolecular chemistry up to now [19,20], whose molecular structures are shown in Scheme 2 as cyclic oligosaccharides composed of glucopyranose units and can be characterized by a truncated cone structure with hydrophobic interior and hydrophilic exterior [21]. They have been used in many fields such as pharmaceutical industry, food technology, biotechnology, cosmetics and catalysis [22–24]. The most notable feature of cyclodextrins is their ability to form host–guest inclusion complexes with a very wide range of compounds by molecular complexation, so that they can enhance the solubility and stability of some guest molecule [25–27].

Isothermal titration calorimetry (ITC) is an extremely powerful and highly sensitive technique that is capable of determining the interaction of reacting species in solution and has hitherto been used with great success in the study of interaction between biomolecules in dilute aqueous solutions both from thermodynamic and from kinetics points of view [28]. In a word, it is of significance to study the interactions of CDs with resveratrol in aqueous system using the method of ITC. In the present work, heat effects caused by interactions of several CDs with resveratrol were determined by ITC and thermodynamic parameters were calculated based on the calorimetric data and were discussed according to the weak interactions between the host and the guest molecules. In order to verify the results acquired from ITC, UV spectra were also determined and analyzed.

2. Experimental

2.1. Materials

Resveratrol was purchased from Xi'an Sino-Herb Biotechnology Company and the stated purity was better than 98%, which was dried under reduced pressure at the temperature of 350 K in order to remove the impurity (mainly ethanol). The molecular structure of resveratrol is provided in Scheme 1. α- and γ-CD were obtained from Aldrich Company and were also

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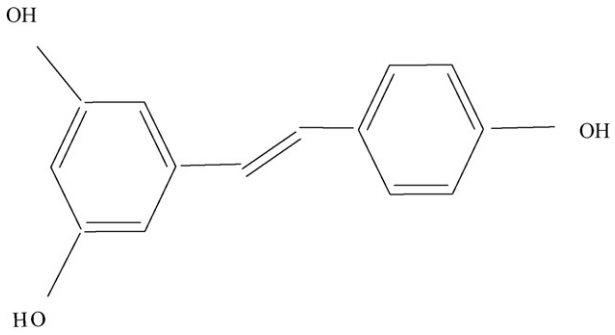


Scheme 1. Molecular structure of resveratrol.

≥98% pure. β- and Mβ-CD were purchased from Shanghai Chemical Reagent Company and purified twice by recrystallization in redistilled water. All of the CD samples were dried under reduced pressure at 358 K for 24 h prior to use. Double distilled water used in the experiment was prepared in the presence of basic potassium permanganate. Mass of each sample was weighed using a Mettler Toledo AG 135 analytical balance with a precision of ±0.01 mg.

2.2. Microcalorimetric measurement

Titration calorimetric measurement was performed by a 201 nanowatt scale isothermal titration microcalorimeter supported by Thermal Activity Monitor TAM 2277 (Thermometric, Sweden), which was controlled by Digitam 4.1 software. This instrument can be electrically calibrated with a precision better than ±1% that was verified by measuring the dilution enthalpy of a concentrated sucrose solution with the literature method [29]. In the experiment, the reaction cell and reference cell of the calorimeter were initially loaded with 500 μL resveratrol solution at 5.21×10^{-4} mol L^{-1} and 750 μL pure water, respectively; the titrant solution was injected into the stirred sample vessel in 30 aliquots of 12 μL using a Hamilton syringe controlled by a 612 Lund Pump. The concentrations of α-, β-, γ- and Mβ-cyclodextrins as titrants were, respectively, 1.46×10^{-3}, 1.43×10^{-3}, 1.40×10^{-3} and 8.42×10^{-4} mol L^{-1}. The interval between two injections was 40 min, which was sufficiently long for the signal to return to the baseline. The system was stirred at 30 rpm with a gold propeller. All experiments were performed at the temperature of 298.15 ± 0.01 K and were started after the baseline became stable so that the heat produced by stir can be automatically deducted. To deduct the dilution heats of resveratrol and CD solution, titration experiments were performed for each of CD solution titrated into the solvent (pure water) and the solvent into resveratrol solution, respectively. All of the dilution heats were found to be negligible.

2.3. UV–vis spectrum determination

An Hp8453 UV–vis spectrophotometer (USA) was used for absorbance determination of solutions. The temperature of the sample was controlled at 298.0 ± 0.1 K. Four kinds of CDs with the concentration of 4.00×10^{-4} mol L^{-1} were added into the resveratrol solution in which the concentration of resveratrol was always at 4.34×10^{-5} mol L^{-1}.

3. Results and discussion

3.1. Thermodynamic data analysis

3.1.1. Analysis process

To evaluate the standard enthalpy of formation for inclusion complex of drug with cyclodextrin in aqueous medium, ΔH_i°, apparent equilibrium constants β_i for overall reactions have been defined as follows:

$$M + iL = ML_i$$

$$\beta_i = \frac{[ML_i]}{[M][L]^i} \quad \Delta H_i^\circ \tag{1}$$

where $i = 1, 2, 3$. In Eq. (1), M or L can represent either guest (Resveratrol) or host (CD), so there are five possible reaction models. The total concentrations of L and M can be obtained according to the following formulas:

$$[M]_0 = [M]\left(1 + \sum \beta_i [L]^i\right) \tag{2}$$

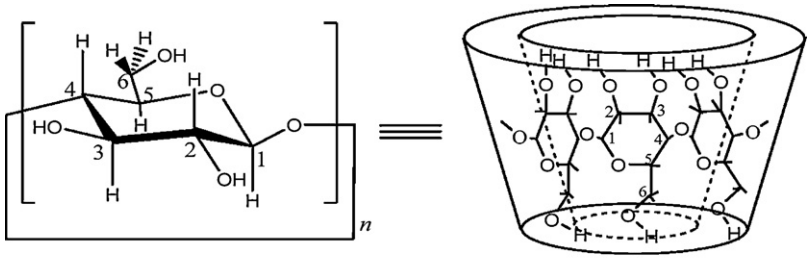
$$[L]_0 = [L]\left(1 + [M]\sum i\beta_i [L]^{(i-1)}\right) \tag{3}$$

The relationship between the overall equilibrium constants, β_i, and the stepwise equilibrium constants, K_i, is given by

$$\beta_i = \prod K_i \tag{4}$$

ΔH_i° and β_i (or K_i) can be obtained by the multi-nonlinear regression equation analysis with the Ligand Binding program of the Digitam 4.1 software. By comparing the congruousness between the simulation curve and the experiment point, the most reasonable result can be obtained as final result. Furthermore, the standard changes of Gibbs free energy (ΔG°) and entropy effect ($T\Delta S^\circ$) of the combination can be derived using the following thermodynamic formulas [30]:

$$\begin{aligned} \Delta G_i^\circ &= -RT \ln \beta_i \\ \Delta G_i^\circ &= \Delta H_i^\circ - T\Delta S_i^\circ \end{aligned} \tag{5}$$



[n = 6 (α -CD), n = 7 (β -CD), n = 8 (γ -CD)]

Scheme 2. Molecular structure of CDs.

Table 1
Thermodynamic parameters of the complexation of host (α-, β-, γ-, Mβ-CD) with guest (RES) in aqueous solution at 298.15 K.

Host	Reaction model	β_i (L/mol)	ΔH° (kJ/mol)	ΔG° (kJ/mol)	$T\Delta S^\circ$ (kJ/mol)
α-CD	M + L = ML	877.24	−27.18	−16.80	−10.38
β-CD	M + L = ML	952.29	−26.16	−17.00	−9.16
γ-CD	M + L = ML	4.74×10^4	−1.50	−26.69	25.19
Mβ-CD	M + L = ML	3054.10	−20.36	−19.89	−0.47

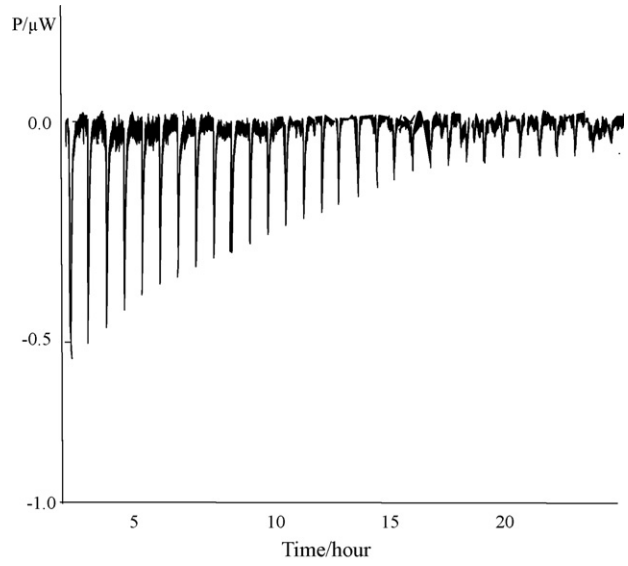


Fig. 1. Variation of heat-flow/electrical power as a function of time, titrant: β-CD (1.43×10^{-3} mol L^{-1}); titrand: RES (5.21×10^{-4} mol L^{-1}).

The relationship between the enthalpy of formation ($\Delta H^\circ{}_i$) and the apparent equilibrium constant (β_i) can be shown by Eq. (6).

$$\Delta H_i^\circ = -RT \ln \beta_i + T\Delta S^\circ \quad (6)$$

The thermodynamic parameters for the resveratrol complexes with several CDs are listed in Table 1, and a typical calorimetric titration plot and a typical fitting curve of the binding complex system are shown in Fig. 1 and Fig. 2, respectively.

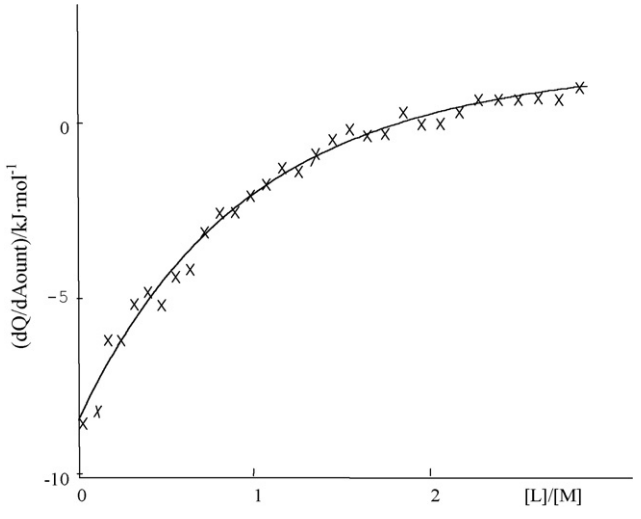


Fig. 2. Rate of change in the heat caused by the host–guest interaction versus the ratio of concentrations [L]/[M]. L and M, respectively, represent β-CD and RES, the points are gotten from experiment and the line is the result of calculated. The concentrations of the titrant and the titrand are, respectively, the same as those in Fig. 1.

3.1.2. Thermodynamic parameters

As shown by the data in Table 1, the four host–guest complexes are all in 1:1 stoichiometry (M + L = ML). The cause might be that the concentrations of CD and resveratrol are rather low in the solution, so there is little opportunity for the host and the guest to form complexes in other stoichiometry. From the values of β_i (=β_1), it could be observed that the inclusion complex of γ-CD with the drug is much more stable than those of other CDs with the drug. This phenomenon can be attributed to the different inner sizes of the hydrophobic cavity of the CDs. The molecular dimension of γ-CD is the largest, so it might be just right for the guest molecule entering into the cavity of γ-CD molecule.

It can be seen from Table 1 that the standard formation enthalpies (ΔH°) of all the CD complexes are negative, i.e., the heat effect is beneficial to the formation of host–guest supramolecular structure. The negative heat effects include the energy released by transferring of water molecules from the holes of completely hydrated CD molecules into the bulk aqueous phase and that caused by hydrophobic interaction between the CD and the drug molecules [31,32]. Assuming that the volume of a water molecule is ~30 å^3, the number of water molecules that per molecule of α-, β-, and γ-CD can accommodate are 6, 9 and 14, respectively [33,34]. It was proposed [35] that they are not able to develop a full hydrogen bonded network inside the cavity, probably due to the high curvature of the inside of the cavity. When the water molecules are released, the hydrogen bonds reform, which leads to a release of heat. ΔH° is less negative for the inclusion compounds formed by the drug with β-CD and Mβ-CD than that formed by the drug with α-CD and much negative than that with γ-CD. This phenomenon may be caused by the incomplete intramolecular hydrogen-bond belt in α-CD molecule, since one glucopyranose unit is in a distorted position [36]. Consequently, the molecular conformation of α-CD can alter to combine with the drug molecule more tightly. So, binding between the interior of α-CD molecule with the hydrophobic part of the drug molecule releases a larger amount of energy. For β-CD or Mβ-CD molecule, they have smaller curvature inside their cavity, to which the water molecules can better adapt. All water molecules are expected to be expelled upon complexation of both β-CD and Mβ-CD with the guest. However, the minimum of the binding enthalpies of γ-CD with drug can be attributed to the retention of the water in the inclusion complex cavity allowing for a 'looseness' of the guest molecule fits into the γ-CD cavity. In a word, the foregoing trend can be well understood by considering all of the factors together.

The entropy effect ($T\Delta S^\circ$) of α-, β-, γ- and Mβ-CD–guest complexes are −10.38, −9.61, 25.19 and −0.47 kJ mol^{-1}, respectively, which are all negative values except for γ-CD–drug complex. In order to explain this tendency, structural factors governing the entropy effect should be taken into account. As mentioned above, the drug molecule possesses hydrophobic groups, benzene ring and hydrocarbyl chain, which can drive water molecules from the molecular cavity of CD to the bulk solvent, this transport of water molecules can cause increase in entropy. Furthermore, collapse of the iceberg structure formed by water molecules around each hydrophobic group also causes the entropy increase when the hydrophobic groups combine with the CD molecule. If only these two entropy-increasing factors were considered, formation of CD

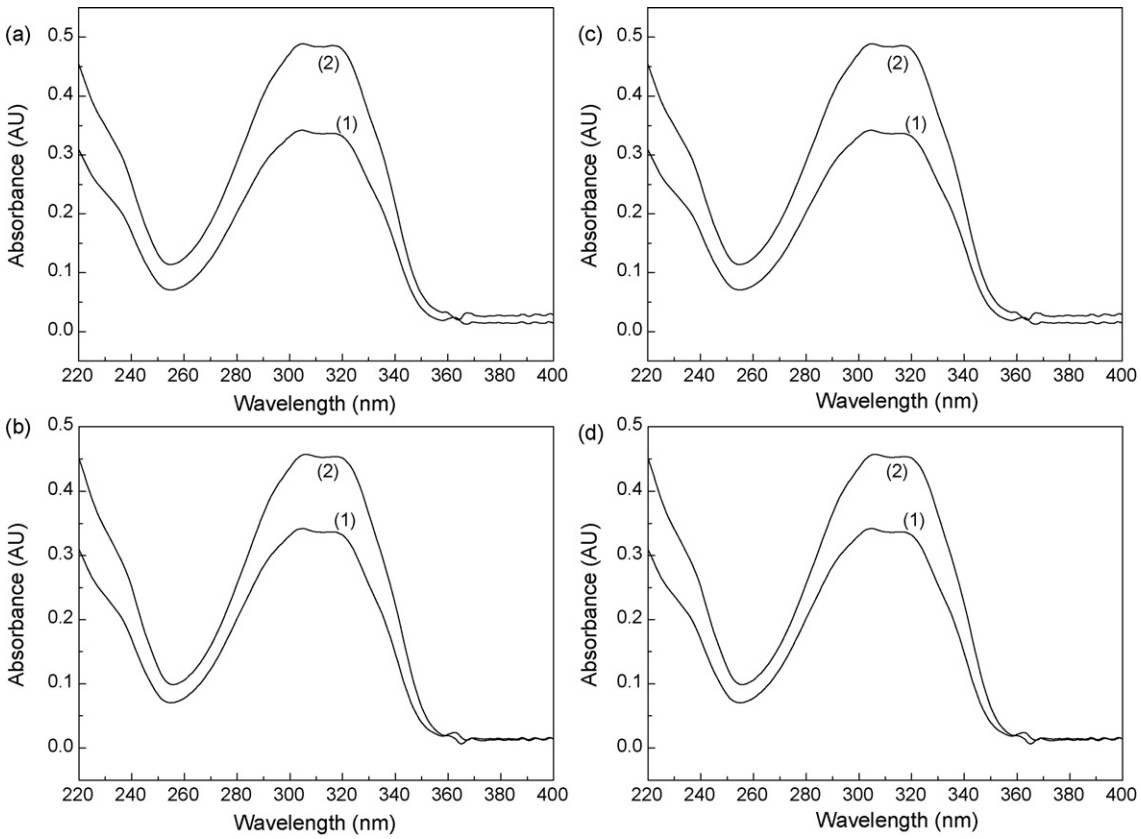


Fig. 3. Influence of CD on the UV–vis spectrum of RES, (a): α-CD; (b): β-CD; (c): γ-CD; (d): Mβ-CD. Curve (1): aqueous solution of RES at 4.34×10^{-5} mol L^{-1}; Curve (2): aqueous solution of RES at 4.34×10^{-5} mol L^{-1} in coexistence with CD at 4.00×10^{-4} mol L^{-1}.

complex with the drug would be an entropy-increasing process. However, there is an important factor causing entropy decrease, that is the directly hydrophobic interaction of molecular hole of CD with the included part of the drug molecule, which makes negative contribution to entropy. From the values of $T\Delta S^{\circ}$, we can deduce that the former influence surpass the later one for the interaction of γ-CD with the drug, while the later influence become dominant for the interactions of α-, β- and Mβ-CD with the drug. The values of $T\Delta S^{\circ}$ also indicate that the order of the contribution of entropy to the formation of inclusion complex is that: γ-CD–drug > Mβ-CD–drug > β-CD–drug > α-CD–drug, which is opposite to the tendency of the enthalpy change. This tendency might be mainly decided by the transfer of water molecules from molecular cavity of CD to the bulk medium. The larger the inner cavity of CD molecule is, the more the water molecules can be driven from the host cavity.

The values of standard Gibbs free energy changes (ΔG°), which are decided by enthalpy changes as well as entropy changes, indicate that all of the inclusion complexes can spontaneously form in aqueous solution. Combining with the values of ΔH° and $T\Delta S^{\circ}$, we can deduce that the complexation processes of α-, β- and Mβ-CD with the drug were shown to be enthalpy favored, while the formation of γ-CD–drug was synergistically driven by enthalpy and entropy.

3.2. Ultraviolet absorption spectra

Fig. 3(a)–(d), respectively, shows the UV spectra of resveratrol in the presence of α-, β-, γ- and Mβ-cyclodextrin. From these figures we can see that the typical absorption peaks of resveratrol center at 306 nm, which is in good accordance with that reported in the literature [18]. When the drug is in coexistence with a CD, the absorption peak becomes higher at almost the same wavelength, this indicate that the host–guest inclusion complex is formed [20]. There is nearly no influence of each of the CDs on the peak wavelength of the drug (Fig. 3), which means that the interaction between the host and the guest is quite weak. The changes in absorbance at the peak wavelength (ΔA) caused by the CDs at the concentration about 10 times of the guest concentration are shown in Table 2. The value of ΔA corresponding to the formation of the α-CD complex with the drug is the largest, showing that its inner surface is most near to the hydrophobic part of the guest, in other words, association force between α-CD and resveratrol is the strongest. This is in accordance with the largest negative formation enthalpy value (Table 1).

Table 2
The changes in absorbance at the peak wavelength (ΔA) caused by the CDs at the concentration about 10 times of the guest concentration, the concentrations of resveratrol and each of the CDs are 4.34×10^{-5} and 4.00×10^{-4} mol L^{-1}, respectively.

Hosts	α-CD	β-CD	γ-CD	Mβ-CD
ΔA	0.160	0.123	0.147	0.116

4. Conclusions

Calorimetric measurement for the interactions of α-, β-, γ- and Mβ-CD with resveratrol at 298.15 K have shown that all of the stoichiometry of the host–guest complex is in 1:1. The complexation processes of α-, β- and Mβ-CD–drug are predominantly enthalpy favored. While γ-CD–drug is mainly enthalpy and entropy driven. The UV–vis spectra can be regarded as evidence for the formation of inclusion complexes.

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