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Combined calorimetric, spectroscopic and microscopic investigation on the inclusion complex from cyclocurcumin and sulfobutylether-β-cyclodextrin in aqueous solution and Kinetics of thermal cis-trans isomerization

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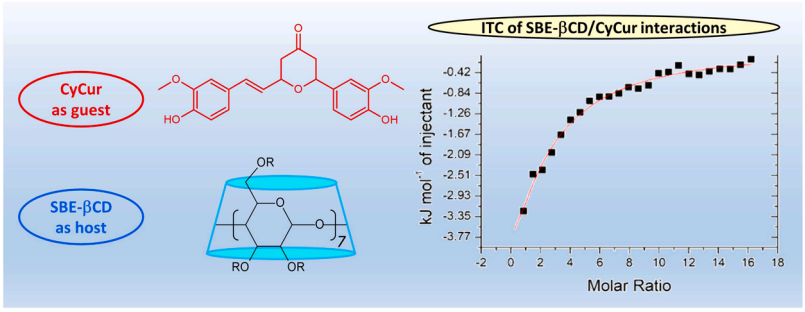
HIGHLIGHTS

- Complexation between cyclocurcumin and sulfobutylether-βCD was studied in aqueous solution.
- Benesi-Hildebrand model was applied to determine stoichiometry and binding constant.
- Thermodynamic parameters were measured by Isothermal Titration Calorimetry.
- Scanning electron and optical microscopy were performed.
- Kinetics of CyCUR cis-trans isomerization in the presence of SBE-βCD was investigated.

GRAPHICAL ABSTRACT



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ABSTRACT

The complexation reaction between cyclocurcumin (CyCur), a natural curcuminoid with bioactive effects, and sulfobutylether-β-cyclodextrin (SBE-βCD), one of the more versatile and tolerate β-cyclodextrin derivates, was investigated in aqueous solution at 298 K. The UV–vis spectral changes of CyCur in the presence of SBE-βCD indicate the formation of the host-guest inclusion complex according to a 1:1 stoichiometry. The binding constant (K_b) determined by applying the Benesi-Hildebrand model was comparable to the value obtained by Isothermal Titration Calorimetry (ITC) measurements. Moreover, the thermodynamic parameters of the SBE-βCD/CyCur interactions demonstrate that the complexation process is enthalpically driven. Interestingly, microscopy analysis highlights the tendency of cyclocurcumin to aggregate into spherical fluorescent structures able to change their aspect and morphology in the presence of SBE-βCD. Finally, the thermal cis-trans isomerization rates of CyCur in the temperature range 294–314 K and the energetic parameters calculated by Arrhenius and Eyring plots were spectroscopically determined in SBE-βCD aqueous solution.

1. Introduction

The formation of host-guest inclusion complexes based on native or modified cyclodextrins represents one of the most efficient methods to increase the aqueous solubility of highly lipophilic molecules in delivery systems or specific devices [1–5]. Cyclodextrins are cyclic

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oligosaccharides formed by D-glucopyranose units α (1,4)-linked in a truncated cone-shaped structures having a hydrophobic cavity and a hydrophilic surface. The most common ones are α-, β-, and γ-cyclodextrins, consisting of six, seven, and eight D-glucopyranose units, respectively. It was observed that non-covalent interactions, as van der Waals forces, hydrogen bonding and electrostatic attraction are involved in the insertion of the guest into the cyclodextrin cavity [6–8]. Generally, the binding constant of the inclusion complex depends on several parameters, such as pH, temperature, concentration, and the presence of cosolvents, while the host:guest ratio mainly depends on the size of the included molecule [9,10]. The appropriate cavity size and the relatively low price make β-cyclodextrin the most used cyclodextrins among the commercially available types. Esterification, etherification, acylation, and alkylation are often performed to increase the water solubility of the cyclodextrin molecule, enhance the complexation capability, and reduce the toxicity [11–13]. In the sulfobutylether-β-cyclodextrin structure (SBE-βCD) the hydroxyl groups of the native cyclodextrin are substituted by average seven negatively charged sulfobutylether groups to obtain an excellent derivate in overcoming the main limits of β-cyclodextrin (Fig. 1). Although the SBE-βCD molecules exhibit enhanced properties as host for neutral and ionic guests in comparison to native and modified β-cyclodextrin, its binding behavior is still marginally reported [14–20].

In this work the interaction of SBE-βCD with cyclocurcumin (CyCur) was investigated. Differently from the other curcuminoids in turmeric, cyclocurcumin bears an α,β-unsaturated dihydropyranone moiety instead of the bis-α,β-unsaturated diketone, so that the keto-enol tautomerism observed for curcumin, demethoxycurcumin, and bisdemethoxycurcumin was replaced by trans-cis photoisomerization [21–23]. It was calculated that the activation energy of the reaction is about 30 kcal/mol, therefore the trans isomer represents the dominant form of cyclocurcumin in nature and in solution [24] (Fig. 1). Although its low content in comparison to the other constituents of turmeric, the photoreactive behavior, the solvatochromism and the immune-modulating, antioxidant, anti-vasoconstrictive, neuroprotective effects of CyCur deserve in-depth investigation to enlarge and optimize its application range [23,25–27]. Herein, the formation of the inclusion complex between SBE-βCD as host and cyclocurcumin as guest was studied according to Benesi-Hildebran method [28,29]. Stoichiometry, binding constant (K_b), and thermodynamic parameters, such as the enthalpy (ΔH°) and entropy (ΔS°) changes were determined in aqueous solution at 298 K. The samples of CyCur, SBE-βCD and SBE-βCD/CyCur were also observed by optical and scanning electron microscopy. The rate of the thermal cis-trans isomerization of CyCur in the presence of SBE-βCD was spectroscopically determined in the temperature range 294–314 K, and the energetic parameters of the reaction, as the activation energy (E_a), the frequency factor (A), the activation enthalpy ($\Delta H^{\neq}$) and the activation entropy ($\Delta S^{\neq}$) were calculated by Arrhenius and Eyring plots.

2. Experimental

2.1. Materials

Cyclocurcumin powder (purity 99 %) was purchased from MuseChem, SBE-βCD sodium salt (average degree of substitution ~ 6.5) was a gift from CycloLab (Cyclodextrin Research & Development Laboratory Ltd., Budapest, Hungary). Ethanol (99 % solvent spectroscopic grade), D_2O 99.9 %, DMSO-d_6 99.9 % were purchased from Sigma-Aldrich. All reagents were used without further purification.

2.2. Sample preparation for spectroscopic analysis

Stock ethanolic solution of CyCur was prepared at a concentration of 3×10^{-3} M and kept in the dark at room temperature. Then, 20 μL of the solution was transferred to 1 cm light path quartz thermostated cuvettes containing 2 mL of aqueous solution at different SBE-βCD concentration.

The stoichiometry and the binding constant (K_b) of the SBE-βCD/CyCur inclusion complex were determined according to Benesi-Hildebran method described by Eqs. (1) and (2):

$$(A\text{-}A_0) = K_b\,\Delta\varepsilon\,[\text{CyCur}]\,[\text{SBE-}\beta\text{CD}] / (1 + K_b\,[\text{SBE-}\beta\text{CD}]) \quad (1)$$

$$[\text{SBE-}\beta\text{CD}]\,[\text{CyCur}] / (A_0\text{-}A) = 1/(K_b\,\Delta\varepsilon) + [\text{SBE-}\beta\text{CD}] / \Delta\varepsilon \quad (2)$$

where A and A_0 are the absorbance intensity of CyCur in the presence and in the absence of SBE-βCD, respectively; Δε is the difference in the molar absorption coefficients for free and complexed CyCur; K_b is the binding constant; [CyCur] and [SBE-βCD] are the total concentration of guest and host, respectively. The spectra of the samples were recorded at 298 K by using a spectrophotometer Jasco V570.

2.3. Sample preparation for ITC analysis

The calorimetric experiments were carried out using the ITC 200 (Northampton, MA). The reference cell and the sample cell of approximately 200 μL are both insulated by an adiabatic shield. The titration was carried out by stepwise injections of 10 mM SBE-βCD aqueous solution from a 40 μL injection syringe into the sample cell filled with 0.1 mM CyCur aqueous solution. The syringe is tailor-made such that the tip acts as a blade-type stirrer to ensure an optimum mixing efficiency at 1000 rpm. An injection schedule was automatically carried out using interactive software after setting up the number of injections, volume of each injection, and time between each injection. All measurements were carried out at a constant temperature of 25 °C. Calorimetric data were processed by the computer program Origin.

2.4. Sample preparation for ^1H NMR analysis

CyCur was dissolved in DMSO-d_6 at the concentration of 6.7×10^{-3} M, then an aliquot was mixed with SBE-βCD in D_2O (in 1:1, 1:2, and 1:3 molar ratio). The samples were kept in DMSO/D_2O 50/50 v/v.

Free CyCur and SBE- βCD were solubilized in the same solvent mixture.

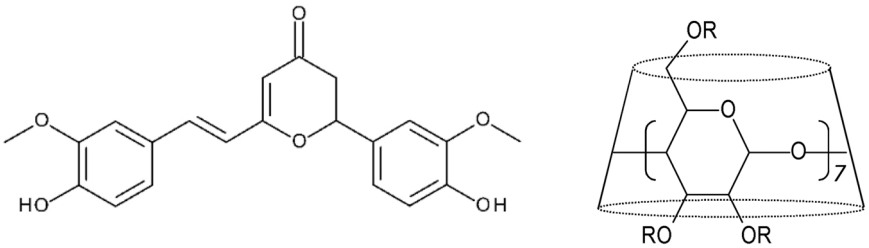


Fig. 1. Structures of cyclocurcumin (on the left), and sulfobutylether-β-cyclodextrin (on the right), where R corresponds to -$CH_2CH_2CH_2CH_2SO_3Na$ or -H and 6.5 is the average degree of substitution.

The spectra were recorded by using a Varian Mercury 300 MHz instrument equipped with VNMRJ 3.2 software. ^{1}H chemical shifts were referred to DMSO.

2.5. Sample preparation for microscopy analysis

Several drops of the CyCur, SBE-βCD, and SBE-βCD/CyCur sample solutions were placed on glass slide and dried at room temperature and atmospheric pressure for 48 h. Then, the samples were analyzed by using a light inverse Zeiss Axiovert microscope (Zeiss, Germany), equipped with Hoffmann optic 40x and a video camera for image detection. Fluorescence images were obtained by using a Zeiss UV filter that excites in the wavelength range 359–371 nm and detects fluorescence at wavelengths >397 nm.

Similarly, for SEM analysis, several drops of the investigated sample solutions were placed on glass slide and dried under vacuum. After 48 h, the samples were carbon-coated and analyzed.

2.6. Sample preparation for the kinetic measurements

An aliquote of the ethanolic stock solution was transferred to 1 cm light path quartz thermostated cuvette containing 2 mL of the SBE-βCD aqueous solution to obtain a CyCur final concentration of 2.0×10^{-5} M. The sample was irradiated for 10 min in the temperature range 294–314 K by using a Hg arc lamp (200 W) equipped with a band-pass interference filter centered at $365.0 + 2/-0$ nm wavelength and $10.0 + 2/-2$ nm bandwidth in order to induce the photoisomerization of cyclocurcumin. The UV–vis spectra were recorded at the investigated temperature by using a spectrophotometer Jasco V570. The decreasing of the high-intensity absorption band and the simultaneous increasing of the peak at lower wavelength were used as evidence for the trans-cis conversion of the sample. The cis-trans conversion was followed by recording the absorption increasing as a function of time, according to a first-order profile. The kinetic rate constant, (k_{obs}), the activation energy (E_a), the pre-exponential factor (A), the activation enthalpy ($\Delta H^{\neq}$), and the activation entropy ($\Delta S^{\neq}$) from Arrhenius and Eyring plot, respectively, were determined as previously described [23].

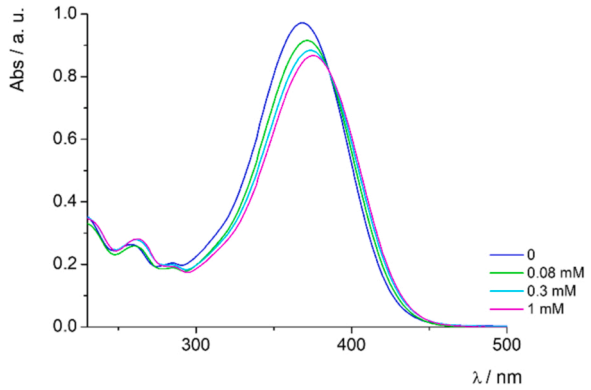


Fig. 2. UV–vis spectra of 3×10^{-5} M CyCur in aqueous solution and in the presence of SBE-βCD from 0.08 to 1 mM.

3. Results and discussion

The UV–vis spectrum of cyclocurcumin in aqueous solution shows a maximum absorption band at 368 nm and weak intensity peaks at 286, 260, and 233 nm, according to the data previously reported [23,24].

It was observed that the conversion of a part of the dominant trans isomer into the cis form under irradiation induces the decreasing of the maximum band and the simultaneous increasing of the peak at 286 nm [23].

In the presence of SBE-βCD the absorbance at 368 nm decreases and shifts to 375 nm but no variation can be observed at 286 nm (Fig. 2), suggesting that CyCur tends to remain as trans isomer in the investigated conditions. Moreover, the bathochromic shift can be considered as evidence of the less polar microenvironment surrounding the guest molecules due to the insertion of CyCur into the hydrophobic cavity of the SBE-βCDs, while the isosbestic point at about 390 nm observed in the UV–vis spectra by increasing the SBE-βCD concentration suggests the 1:1 stoichiometry for the CyCur:SBE-βCD inclusion complex in the investigated conditions [29,30].

The Benesi-Hildebrand plot of the difference between the absorbance of CyCur in the presence (A) and in the absence (A_0) of SBE-βCD versus the concentration of the cyclodextrin in solution was reported in Fig. 3 (a). The non-linear fitting implies a 1:1 inclusion complex [28] and the K_b value of 2848 M^{-1} was determined. Further evidence for the stoichiometry of the investigated complex was obtained by the linear fitting [29] reported in Fig. 3(b) by which the K_b value of 2435 M^{-1} was obtained.

Generally, binding constants in the range 10–4000 M^{-1} are associated to inclusion complexes involving cyclodextrins and the relatively low K_b obtained in the case of the SBE-βCD/CyCur complex represents a potential advantage suggesting an efficient release of cyclocurcumin from the cyclodextrin cavity [31]. The complete thermodynamic profile of the interactions involved between the investigated host and guest in aqueous solution at 298 K was provided by ITC measurements (Fig. 4).

The thermodynamic parameters of the complexation of SBE-βCD and CyCur were reported in Table 1.

The K_b obtained by the ITC measurements is comparable to the values spectroscopically determined from Eqs. (1) and (2), assuming the

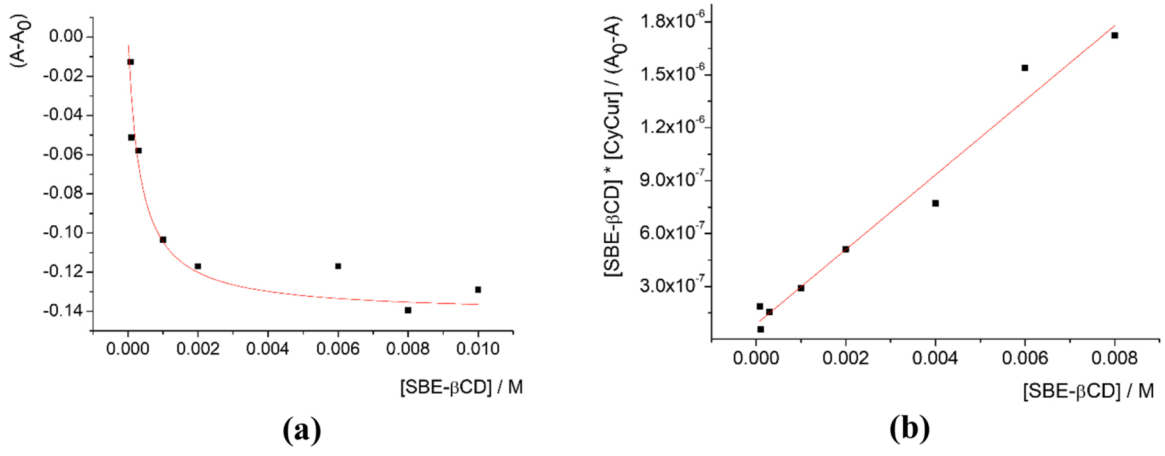


Fig. 3. Non-linear (a) and linear (b) Benesi-Hildebrand plots for the investigated complex.

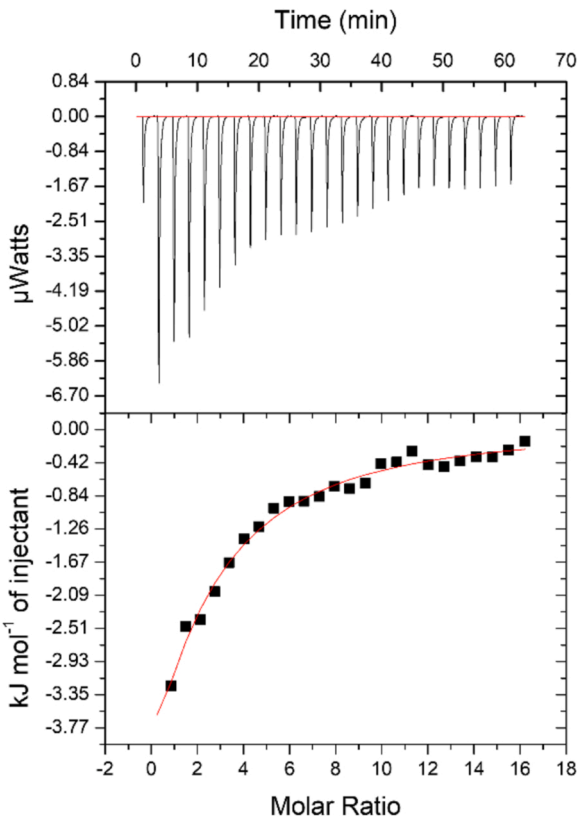


Fig. 4. Isothermal titration calorimetry profiles for the investigated complexation in aqueous solution at 298 K. The upper panel represents the raw data for the titration of successive aliquots of SBE-βCD into CyCur solution. The bottom panel represents the integrated heat data after correction of the heat of dilution.

Table 1
Thermodynamic parameters of the investigated complex.

K_b (M^{-1})	ΔH° (kJ/mol)	ΔS° (J/mol·K)	ΔG° (kJ/mol)
2000 ± 106	-22.4 ± 0.6	-11.7	-18.8

1:1 stoichiometry for the inclusion complexation. Negative values of ΔH° and ΔS° were determined in the investigated conditions according to the enthalpic and entropic changes commonly observed in binding involving cyclodextrins [8,32,33]. Negative ΔH° describes the exothermic process associated to concomitant effects, such as the insertion of the guest and the resulting displacement of water molecules from the cavity of cyclodextrin, the generation of van der Waals forces, hydrogen bonds and electrostatic interactions; negative ΔS° reflects the endothermic process by which the translational and rotational degrees of freedom of the complexed guest are decreased in comparison to the free ones and, simultaneously, the hydration layer on the host surface were destroyed by the complexation [34]. In the SBE-βCD/CyCur solution, the inclusion of CyCur into the cavity of SBE-βCD is enthalpically driven ($\Delta H^\circ = -22.4$ kJ/mol) and entropy opposed ($\Delta S^\circ = -11.7$ J/mol·K). Moreover, the calculated Gibbs free energy (−18.8 kJ/mol) demonstrates that the SBE-βCD/CyCur complexation is a spontaneous reaction [35]. It was previously observed that the decreasing of the hydrophobic interactions between the SBE-βCD and some drugs may depend on the hydrated sulfonated groups by which distortion of the cyclodextrin cone and inhibition of the guest insertion in the cyclodextrin cavity occur [36]. In the case of cyclocurcumin complexation the thermodynamic data suggest that the exotermic process is dominant on the endothermic process in the investigated conditions.

^{1}H NMR analysis confirms the formation of the inclusion complex in solution showing changes of the chemical shifts for some cyclocurcumin protons in the presence of SBE-βCD in 1:1, 2:1, 3:1 host:guest molar ratio as reported in Table 2.

Increasing the amount of SBE-βCD, the protons 1,4, 7, the aromatic 5' and 5'' were shifted downfield, whereas the olefinic proton 6 was shifted upfield, suggesting that whole CyCur molecule is involved in widespread interaction with the host [37 38].

The microscopy analysis was also performed. The CyCur sample reveals the tendency of the molecule to aggregate into spherical structures detectable under visible light and in fluorescence as observed in the optical micrograph reported in Fig. 5.

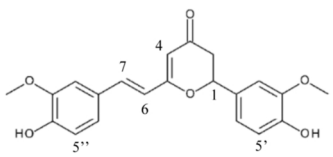
In the case of SBE-βCD sample no aggregates or fluorescence can be observed (see Supplementary materials), while significant changes in the structures can be highlighted in the SBE-βCD/CyCur sample in carbon coated SEM samples as shown in Fig. 6.

The first-order rate constants (k_{obs}) of the CyCur cis-trans isomerization in the presence of SBE-βCD measured in the temperature range 294–314 K and the energetic parameters of the reaction were reported in Table 3 (a) and (b), respectively.

Rising temperature from 294 to 314 K promotes the CyCur cis-trans isomerization rate in the SBE-βCD aqueous solution, according to the trend previously observed in pure water [23]. In particular, the presence of the SBE-βCD slightly increases the k_{obs} value. It was observed that both E_a and $\Delta H^{\#}$ depend on the solute–solvent interactions involved in the initial state of the thermal cis–trans isomerization that consists in the solvation of the cis isomer [39]. The lower value of E_a and $\Delta H^{\#}$ in SBE-βCD aqueous solution (69.9 and 67.4 kJ/mol, respectively) compared to the data in pure water (75.2 and 72.7 kJ/mol, respectively) confirm that the host-guest interactions exists also after the photoconversion of CyCur into the less stable cis isomer promoting an efficient solvatation of the guest.

Generally, the pre-exponential factor A is associated with entropy.

Table 2
Shifts of CyCur protons in the presence of SBE-βCD at different host-guest molar ratios. The Δδ is the difference between the δ of the inclusion complex and the δ of free CyCur.



Proton Number	Δδ SBE-βCD:CyCur 1:1	ΔδSBE-βCD:CyCur 2:1	Δδ SBE-βCD:CyCur 3:1
7	0.0020	0.0030	0.0035
6	-0.0020	-0.0055	-0.0095
5"	0.0030	0.0055	0.0070
5'	0.0010	0.0025	0.0040
4	0.0010	0.0010	0.0020
1	0.0050	0.0080	0.0090

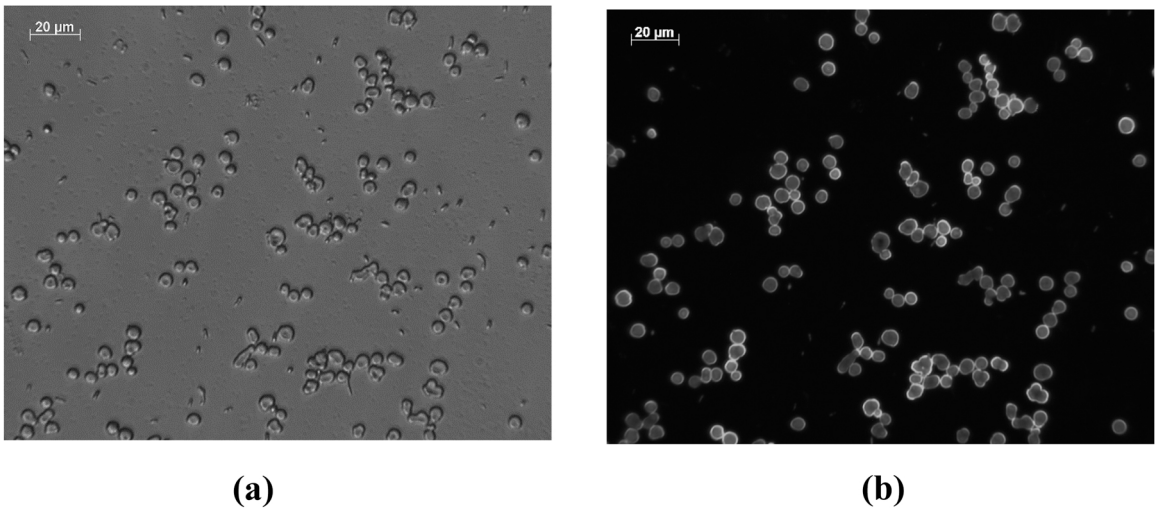


Fig. 5. Optical micrograph of CyCur under visible light (a) and in fluorescence (b).

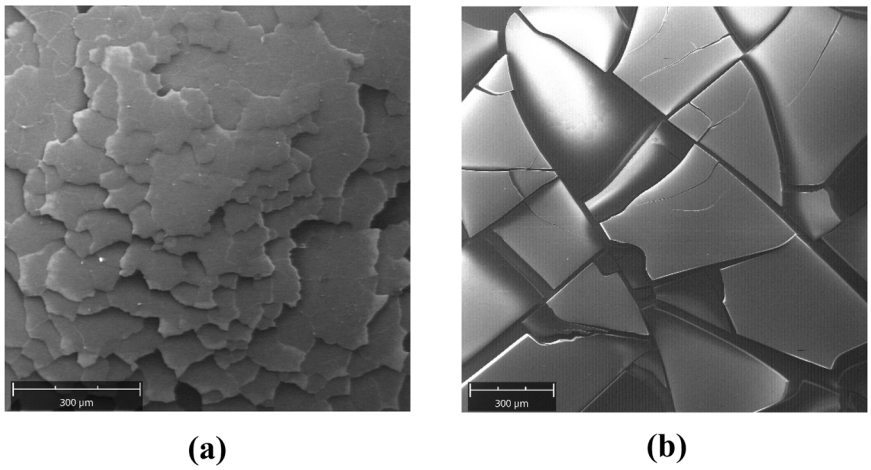


Fig. 6. SEM micrograph of SBE-βCD/CyCur (a) and SBE-βCD (b).

Table 3
(a) Kinetic rate constant values (k_{obs}) of the CyCur cis-trans isomerization in SBE-βCD aqueous solution; (b) Activation energy (E_a), pre-exponential factor (A), activation enthalpy ($\Delta H^{\#}$) and activation entropy ($\Delta S^{\#}$) of the reaction calculated from Arrhenius and Eyring plots.

(a)		(b)	
T (K)	k_{obs} (10^{-3} s^{-1})	Energetic parameters	SBE-βCD/CyCur
294 (± 0.1)	1.89 (± 0.1)	E_a/kJ mol^{-1}	69.9
298 (± 0.1)	2.76 (± 0.1)	A/s^{-1}	4.9×10^9
302 (± 0.1)	4.16 (± 0.1)	$\Delta H^{\#}$/kJ mol^{-1}	67.4
306 (± 0.1)	5.91 (± 0.2)	$\Delta S^{\#}$/JK^{-1} mol^{-1}	-67.8
310 (± 0.1)	8.42 (± 0.1)		
314 (± 0.1)	11.5 (± 0.1)		

The large negative $\Delta S^{\#}$ measured in the presence of SBE-βCD suggests that the transition state of the cis-trans isomerization is considerably more ordered in comparison to pure water [40,41].

4. Conclusions

The formation of an innovative inclusion complex from CyCur as guest and SBE-βCD as host in aqueous solution was studied. The binding constant spectroscopically measured is comparable to the value calorimetrically determined according to the 1:1 stoichiometry. Negative ΔH° change along with negative ΔS° change highlight that the SBE-βCD/CyCur complexation is enthalpically driven.

Further evidence of the formation of the inclusion complex in solution was obtained from 1H NMR spectra.

Microscopy analysis points out the tendency of cyclocurcumin to aggregate in fluorescent spherical structures, changing their shape and morphology in the presence of SBE-βCD.

The thermal cis-trans isomerization of CyCur in the SBE-βCD aqueous solution highlights that interactions host-guest occur also in the presence of CyCur in the cis state.

To the best of our knowledge the results reported herein are unprecedented and could provide promising insights for the development of inclusion-based supramolecular systems.

Supplementary Information

Titrations of CyCur in pure water; titration of CyCur in SBE-βCD aqueous solution; optical micrograph of the SBE-βCD sample; SEM image of the CyCur sample; Kinetic profile of the CyCur cis-trans isomerism in SBE-βCD aqueous solution at 298 K; the Arrhenius and Eyring plots of the reaction in the temperature range 294–314 K; ^{1}H NMR spectra of the CyCur, SBE-βCD, and SBE-βCD/CyCur complex; UV–vis spectra of trans CyCur and cis CyCur detemined by HPLC-DAD are available as Supplementary material.

CRediT authorship contribution statement

Carla Gasbarri: Conceptualization, Investigation, Visualization, Writing – original draft, **Guido Angelini**: Methodology, Formal analysis, Investigation, Data Curation, Resources.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

Data will be made available on request.

Acknowledgments

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.colsurfa.2023.131149.

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