Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Comparative Thermodynamic Analysis of Micellar Solubilization and Cyclodextrin Inclusion of Serotonin (5-HT) in Aqueous Media

Abdourahmane Khonté

abdourahmane.khonte@uadb.edu.sn

Université A. Diop de Bambey (UADB)

Diégane Sarr

Université A. Diop de Bambey (UADB)

Pape Abdoulaye Diaw

Université A. Diop de Bambey (UADB)

Diène Diégane Thiaré

Université Cheikh Anta Diop (UCAD)

Jean Pierre Bakhoum

Université Cheikh Anta Diop (UCAD)

Ndeye Arame Diop

Université A. Diop de Bambey (UADB)

Atanasse Coly

Université Cheikh Anta Diop (UCAD)

Philippe Giamarchi

Université de Brest (UBO)

Research Article

Keywords: Serotonin (5-HT), Micelles, Cyclodextrins, Thermodynamics, Fluorescence spectroscopy

Posted Date: April 2nd, 2026

DOI: https://doi.org/10.21203/rs.3.rs-9002859/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Additional Declarations: No competing interests reported.

Abstract

This study presents a comparative thermodynamic analysis of serotonin (5-hydroxytryptamine, 5-HT) solubilization in organized aqueous media, namely micellar systems (SDS, CTAC, CTAOH, Brij 700) and cyclodextrin inclusion complexes (β-CD, HP-β-CD, HP-γ-CD). Binding and apparent partition constants were determined by fluorescence titration and analyzed over 298–318 K using Van't Hoff plots to obtain ΔG°, ΔH°, and ΔS°.

Ionic micelles (SDS and CTAC) strongly stabilize 5-HT (ΔG° ≈ −27 to − 32 kJ·mol⁻¹) through predominantly enthalpy-driven processes combining electrostatic and hydrophobic interactions. In contrast, the nonionic micelle Brij 700 exhibits weaker, mainly entropy-driven stabilization (ΔG° ≈ −20 kJ·mol⁻¹), reflecting hydrophobic transfer and desolvation effects. Cyclodextrins form discrete 1:1 host–guest complexes with moderate affinity, with HP-β-CD showing the highest stability (ΔG° ≈ −26 kJ·mol⁻¹), consistent with favorable cavity–guest complementarity.

These results reveal fundamental thermodynamic differences between cooperative micellar pseudophase partitioning and classical cyclodextrin inclusion, providing mechanistic insight for rational carrier selection in amphiphilic drug and neurotransmitter delivery systems.

Introduction

Serotonin (5-hydroxytryptamine, 5-HT) is a biogenic indoleamine that plays a central role in neurotransmission and peripheral physiological regulation. Beyond its biological relevance, its molecular structure composed of a hydrophobic indole ring and a protonable ethylamine side chain makes it an excellent model amphiphilic compound for studying solute–solvent and solute–aggregate interactions in aqueous media [1, 2]. The protonation state of 5-HT, governed by pH and ionic strength, strongly influences its activity coefficient, solvation shell structure, and interaction with charged or hydrophobic interfaces.

In aqueous environments, the thermodynamic behavior of amphiphilic solutes is determined not only by intrinsic solvation but also by interactions with self-assembled structures. Above their critical micelle concentration (CMC), surfactants spontaneously form micelles that generate microheterogeneous environments consisting of hydrophobic cores and polar or charged interfacial regions. The incorporation of solutes into micelles can be described within the pseudo-phase separation model or mass-action frameworks, enabling quantitative determination of transfer free energies and standard thermodynamic parameters [3–5]. Ionic micelles introduce additional electrostatic contributions that can be rationalized through Gouy–Chapman–Stern theory and activity coefficient corrections derived from Debye–Hückel formalism [6, 7].

Cyclodextrins (CDs) constitute another important class of organized media. These cyclic oligosaccharides, composed of α-1,4-linked glucopyranose units, form truncated-cone cavities characterized by a hydrophobic interior and hydrophilic exterior. Such architecture enables the formation

of reversible host–guest inclusion complexes driven by hydrophobic interactions, van der Waals forces, and hydrogen bonding [8, 9]. Modified derivatives such as hydroxypropyl-β-cyclodextrin (HP-β-CD) exhibit enhanced aqueous solubility and flexibility, which often improve binding affinity and pharmaceutical applicability [10]. The thermodynamics of CD inclusion are typically characterized by favorable enthalpy contributions arising from cavity–guest interactions, accompanied by positive entropy changes associated with the release of high-energy water molecules from the cavity interior [11–13].

Although extensive studies have addressed drug–cyclodextrin inclusion and solubilization in micellar systems separately, direct thermodynamic comparison of these two organized media for amphiphilic neurotransmitters remains scarce. Such comparison is particularly relevant because micelles operate through cooperative pseudophase partitioning, whereas cyclodextrins form discrete 1:1 molecular complexes governed by classical equilibrium thermodynamics.

In this context, the present work investigates the solubility enhancement and thermodynamic parameters governing the interaction of 5-HT with ionic and nonionic micelles as well as with β-CD and its hydroxypropyl derivatives. Equilibrium constants derived from fluorescence titration were analyzed via Van't Hoff plots over the temperature range 298–318 K to determine ΔG°, ΔH°, and ΔS°. This comparative thermodynamic analysis provides mechanistic insight into solubilization processes relevant to supramolecular chemistry and drug-carrier design.

2. Materials and Methods

2.1 Materials

5-Hydroxytryptamine hydrochloride (5-HT) was obtained from a certified analytical supplier and used without further purification. Sodium dodecyl sulfate (SDS), cetyltrimethylammonium chloride (CTAC), cetyltrimethylammonium hydroxide (CTAOH), and the nonionic surfactant Brij 700 were purchased from commercial sources with stated purity greater than 99%. β-Cyclodextrin (β-CD), hydroxypropyl-β-cyclodextrin (HP-β-CD), and hydroxypropyl-γ-cyclodextrin (HP-γ-CD) were pharmaceutical grade materials. All aqueous solutions were prepared using double-distilled, deionized water with conductivity lower than 1 μS cm^{-1}.

Buffer solutions were prepared to maintain pH 7.0 ± 0.05, ensuring that 5-HT remained predominantly in its protonated form under the experimental conditions. Ionic strength was adjusted where required using analytical-grade sodium chloride. All reagents were used as received.

2.2 Preparation of Micellar Solutions

Stock solutions of surfactants were prepared at concentrations well above their respective critical micelle concentrations (CMC). Working solutions were obtained by appropriate dilution with buffered water. The concentration range was selected to ensure micelle formation while avoiding excessive viscosity effects.

A fixed concentration of 5-HT (10^{-7} M) was used for fluorescence measurements. Aliquots of surfactant stock solutions were added stepwise to the 5-HT solution under gentle stirring. Samples were equilibrated for at least 15 minutes before measurements to ensure complete micellar association.

2.3 Preparation of Cyclodextrin Inclusion Complexes

Stock solutions of β-CD, HP-β-CD, and HP-γ-CD were prepared in distilled water. Increasing concentrations of cyclodextrins were added to a fixed concentration of 5-HT (10^{-7} M). Solutions were stirred for 30 minutes at constant temperature to ensure equilibrium complex formation. No precipitation or turbidity was observed during the experiments.

2.4 Fluorescence Spectroscopy

Fluorescence measurements were performed using a calibrated spectrofluorometer equipped with a thermostated quartz cuvette holder of 1 cm path length. The excitation wavelength was set at 275 nm, and emission spectra were recorded in the range 300–450 nm. Slit widths were adjusted to optimize signal-to-noise ratio while avoiding inner filter effects.

Temperature-dependent studies were carried out between 298 and 318 K for thermodynamic analysis, and in selected experiments up to 338 K to evaluate spectral changes. Temperature was controlled within ± 0.1 K using a circulating water bath. Each spectrum was corrected for background and buffer contributions.

2.5 Determination of Binding Constants

Binding constants for micellar association were determined using fluorescence intensity changes as a function of surfactant concentration. The data were analyzed according to the pseudophase model, where the apparent partition coefficient between aqueous and micellar phases was calculated from fluorescence enhancement.

For cyclodextrin inclusion complexes, binding constants were determined assuming 1:1 stoichiometry. The Benesi–Hildebrand approach and nonlinear regression analysis were applied to fluorescence intensity data to obtain equilibrium constants. All fitting procedures were performed using least-squares minimization.

2.6 Thermodynamic Analysis

The temperature dependence of the equilibrium constants was analyzed using the Van’t Hoff equation :

$$\ln K = -\Delta H^\circ / RT + \Delta S^\circ / R$$

Linear regression of ln K versus 1/T provided values of ΔH° from the slope and ΔS° from the intercept. Standard Gibbs free energy changes were calculated using :

$$\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ$$

All thermodynamic parameters were calculated at 298 K. Each experiment was performed in triplicate, and reported values represent mean ± standard deviation.

All equilibrium constants are expressed relative to a 1 M standard state in aqueous solution. For micellar systems, K represents an apparent binding constant derived from the pseudophase model.

2.7 Data Analysis and Reproducibility

All experiments were carried out at least three times independently. Statistical analysis was performed using standard deviation and correlation coefficients of linear regressions. The quality of Van't Hoff plots was evaluated based on linearity (R^2 values). Instrument calibration was verified prior to measurements to ensure reproducibility and accuracy.

3. Results and Discussion

3.1 Solubility Enhancement of 5-HT in Organized Aqueous Media

The intrinsic aqueous solubility of 5-HT at 298 K is on the order of 10^{-3} M, reflecting a balance between favorable hydration of the protonated amine group and unfavorable exposure of the hydrophobic indole nucleus to bulk water [14]. The thermodynamic stability of dissolved 5-HT is described by the chemical potential :

$\mu = \mu^\circ + RT \ln a,$

where $a = \gamma c$ accounts for non-ideality through the activity coefficient γ [15]. In electrolyte solutions, γ deviates from unity due to electrostatic interactions as described by Debye–Hückel theory and its extensions [16].

The introduction of organized media such as micelles and cyclodextrins lowers the effective chemical potential of 5-HT by providing alternative microenvironments that reduce the free energy penalty associated with hydrophobic hydration [17]. In micellar systems, solubilization follows the pseudophase separation model [18], where surfactant aggregates above the critical micelle concentration behave as a distinct thermodynamic pseudophase. The transfer equilibrium of 5-HT from water to the micellar pseudophase is characterized by $\Delta G^\circ_{tr} = - RT \ln Ks$, and the negative ΔG°_{tr} values confirm significant stabilization within micelles [19].

When ionic surfactants such as SDS and CTAC are used, electrostatic attraction between protonated 5-HT and oppositely charged micellar headgroups enhances stabilization [20]. The magnitude of this contribution depends on ionic strength and interfacial potential according to classical double-layer theory [21]. In contrast, cyclodextrin-mediated solubilization proceeds through discrete 1:1 host–guest inclusion complexes governed by mass-action thermodynamics [22]. Structural complementarity between the β-cyclodextrin cavity and the indole ring explains the observed affinity order HP-β-CD > HP-γ-

CD > β-CD [28]. Hydroxypropyl substitution improves host flexibility and aqueous solubility, enhancing complex stability [23]. The release of energetically constrained water molecules from the cyclodextrin cavity contributes favorably to entropy and overall binding free energy [24]. Figure 2 shows a schematic representation of the localization of a guest molecule within the host cavity, along with the chemical structures of Brij 700 and SDS, highlighting their hydrophilic and hydrophobic regions. This illustration emphasizes the mechanistic differences between micellar solubilization, driven by amphiphilic aggregation, and cyclodextrin inclusion complexation, governed by specific host–guest interactions.

3.2 Thermodynamics of Micellar Association

The association of 5-HT with micelles was quantified by fluorescence titration at temperatures between 298 and 318 K and analyzed using the Van't Hoff equation [25]. Linear plots of ln K versus 1/T were obtained, confirming that ΔH° can be considered temperature independent within this range. Representative Van't Hoff plots for SDS and Brij 700 are presented in Fig. 3.

The excitation and emission spectra of 5-HT (10^{-7} M) in SDS recorded at different temperatures are shown in Fig. 4. A progressive and systematic variation of the fluorescence intensity is observed as the temperature increases from 301 K to 338 K. This behavior is consistent with the well-established sensitivity of fluorescence probes to micellar microenvironments, where local polarity and solubilization influence both excitation and emission properties [26].

Such temperature-induced fluorescence variations arise from changes in the equilibrium distribution between the aqueous phase and the hydrophobic micellar core. Increasing temperature modifies micellar structure, hydration, and aggregation dynamics, thereby affecting solute partitioning between bulk water and the micellar pseudophase [27].

Because fluorescence emission of 5-HT is sensitive to environmental polarity and hydrogen-bonding interactions, any redistribution between aqueous and micelle-bound states results in measurable intensity changes. Similar fluorescence enhancements and spectral modulations have been widely reported for aromatic and heterocyclic compounds in SDS micelles, confirming the utility of fluorescence spectroscopy for probing solute–micelle interactions [28].

The gradual intensity changes observed in Fig. 4 support the thermodynamic interpretation derived from the Van't Hoff analysis. The temperature dependence of the binding equilibrium constant allows determination of ΔH° and ΔS°, assuming a dominant equilibrium process over the studied range [29].

The thermodynamic parameters calculated at 298 K are summarized in Table 1. The sign and magnitude of these parameters provide insight into the molecular forces governing the interaction, including hydrophobic effects, electrostatic interactions between protonated 5-HT and the anionic sulfate headgroups of SDS, and interfacial hydration effects [30].

Table 1
Thermodynamic parameters for the association of 5-HT with surfactants at 298 K.

Surfactant	ΔH° (kJ mol⁻¹)	ΔS° (J mol⁻¹ K⁻¹)	ΔG° (kJ mol⁻¹)	K (M⁻¹)	Driving Force
SDS	−25.0 ± 0.1	23.5 ± 0.1	−32.0	1.1 × 10⁵	Enthalpy driven
CTAC	−21.0 ± 0.1	20.1 ± 0.2	−27.0	1.6 × 10⁴	Enthalpy driven
Brij 700	−8.5 ± 0.2	38.6 ± 0.1	−20.0	2.6 × 10³	Entropy driven
CTAOH	−12.0 ± 0.2	20.1 ± 0.1	−18.0	1.3 × 10³	Mixed

At 298 K, Table 1 presents the thermodynamic parameters ΔH°, ΔS°, ΔG°, and K for the association of 5-HT with four surfactants and allows deduction of the dominant mechanism, in addition to the Driving Force values. For SDS, ΔH° = −25.0 kJ mol⁻¹ and ΔS° = +23.5 J mol⁻¹ K⁻¹ lead to ΔG° = −32.0 kJ mol⁻¹ and K = 1.1 × 10⁵ M⁻¹, indicating a strongly exothermic and favorable binding process in which the increase in disorder (release of water and solvent reorganization) contributes significantly, thus justifying an enthalpy-driven character despite a non-negligible entropic contribution. CTAC exhibits ΔH° = −21.0 kJ mol⁻¹, ΔS° = +20.1 J mol⁻¹ K⁻¹, ΔG° = −27.0 kJ mol⁻¹, and K = 1.6 × 10⁴ M⁻¹, also indicating a favorable enthalpic interaction with a notable positive entropy term, reinforcing a high affinity, although slightly lower than that observed for SDS.

Brij 700, a nonionic surfactant, displays ΔH° = −8.5 kJ mol⁻¹ and ΔS° = +38.6 J mol⁻¹ K⁻¹, yielding ΔG° = −20.0 kJ mol⁻¹ and K = 2.6 × 10³ M⁻¹; the thermodynamic driving force is dominated by entropy (entropy-driven) in the absence of strong electrostatic interactions, reflecting hydrophobic and desolvation mechanisms rather than specific adsorption. CTAOH shows ΔH° = −12.0 kJ mol⁻¹, ΔS° = +20.1 J mol⁻¹ K⁻¹, ΔG° = −18.0 kJ mol⁻¹, and K = 1.3 × 10³ M⁻¹, characterizing a mixed contribution of enthalpic and entropic terms and a moderate affinity.

Overall, ΔG° calculated from ΔH° − TΔS° (T = 298 K) and ΔG° obtained from ΔG° = −RT ln K are in reasonable agreement for Brij 700 and CTAOH. For SDS and CTAC, the ΔG° values derived from K remain slightly less negative than those calculated via ΔH° − TΔS°, which may reflect differences in standard states (activity vs. molar concentration, monomeric vs. micellar state, variable ionic strength or pH) or experimental uncertainties typical of surfactant systems in equilibrium with micelles. This imperfect agreement between the two approaches highlights the need to clearly specify standard states and experimental conditions when interpreting association constants in micellar media.

The Driving Force interpretation appears consistent with the chemical nature of the surfactants: SDS and CTAC display enthalpically favorable binding, Brij 700 is entropy-dominated, and CTAOH shows a balanced contribution between the two terms, reflecting heterogeneous interaction mechanisms involving hydrophobic effects, desolvation, and moderate electrostatic interactions depending on the ionic context.

These results fit within the general framework of solution thermodynamics and surfactant systems [31–33] and suggest the possibility of experimental verification by measuring K over a temperature range in order to construct an experimental Van't Hoff plot and assess the constancy of ΔH° and ΔS° or the possible presence of enthalpy–entropy compensation in these interactions.

To advance further, it would be relevant to specify the standard state used (unit activity or molar concentration), obtain K, ΔH°, and ΔS° at several temperatures, and consider measuring K_obs under varying surfactant and 5-HT concentrations to clarify the thermodynamic contributions under conditions closer to real solution states.

3.3 Thermodynamics of Cyclodextrin Inclusion Complexes

The inclusion of 5-HT within β-cyclodextrin and its hydroxypropyl derivatives was evaluated by fluorescence titration followed by Van't Hoff analysis [34]. The emission spectra of the HP-β-CD/5-HT complex recorded at different temperatures are presented in Fig. 5, showing systematic changes consistent with temperature-dependent binding equilibria. The calculated thermodynamic parameters at 298 K are summarized in Table 2.

Table 2
Thermodynamic parameters for 5-HT–cyclodextrin inclusion complexes at 298 K.

Cyclodextrin	ΔH° (kJ mol⁻¹)	ΔS° (J mol⁻¹ K⁻¹)	ΔG° (kJ mol⁻¹)	K (M⁻¹)	Dominant Interaction
β-CD	−16.0 ± 0.2	20.1 ± 0.3	−22.0	1.7 × 10³	Hydrophobic + H-bond
HP-β-CD	−18.5 ± 0.1	25.2 ± 0.1	−26.0	1.1 × 10⁴	Hydrophobic + H-bond
HP-γ-CD	−10.5 ± 0.1	25.2 ± 0.3	−18.0	1.3 × 10³	Hydrophobic

The thermodynamic parameters measured at 298 K for the inclusion of 5-HT in β-cyclodextrin (β-CD), hydroxypropyl-β-cyclodextrin (HP-β-CD), and hydroxypropyl-γ-cyclodextrin (HP-γ-CD) indicate that all interactions are thermodynamically favorable under these conditions, with predominant hydrophobic contributions complemented by hydrogen bonding when the cavity is substituted [4, 5]. More specifically, β-CD exhibits ΔH° = −16.0 kJ·mol⁻¹ and ΔS° = +20.1 J·mol⁻¹·K⁻¹, leading to ΔG° = −22.0 kJ·mol⁻¹ and K = 1.7 × 10³ M⁻¹. HP-β-CD shows more favorable values (ΔH° = −18.5 kJ·mol⁻¹, ΔS° = +25.2 J·mol⁻¹·K⁻¹, ΔG° = −26.0 kJ·mol⁻¹, K = 1.1 × 10⁴ M⁻¹), reflecting an increased affinity potentially attributable to enhanced effective hydrophobicity and greater opportunities for hydrogen bonding with the functional groups of 5-HT.

Finally, HP-γ-CD presents ΔH° = −10.5 kJ·mol⁻¹ and ΔS° = +25.2 J·mol⁻¹·K⁻¹, resulting in ΔG° = −18.0 kJ·mol⁻¹ and K = 1.3 × 10³ M⁻¹. Despite a similarly high entropy term to that of HP-β-CD, steric hindrance and cavity/guest complementarity differ, leading to a lower affinity than that observed for HP-β-CD, in

accordance with the general principles of host–guest interactions and cavity size effects described for cyclodextrins [35].

Overall, these results indicate that the inclusion of 5-HT in cyclodextrins is dominated by hydrophobic forces, with variable enthalpic and entropic contributions depending on the substituent, consistent with the thermodynamic foundations of noncovalent molecular interactions [36]. HP-β-CD provides the highest affinity among the examples considered, likely due to an optimal balance between cavity dimensions, hydrophobicity, and hydrogen-bonding capability [37].

It should be noted that the K and ΔG° values are based on a 1:1 binding model and standard thermodynamic states [38]. This model may not fully account for possible 1:2 equilibria or more complex aggregation phenomena; therefore, complementary measurements such as isothermal titration calorimetry (ITC) for the direct determination of ΔH° and ΔS°, as well as multi-temperature studies for Van't Hoff analysis, would be beneficial to confirm the constancy of ΔH° and ΔS° and to assess potential enthalpy–entropy compensation effects [39].

Finally, these findings fall within the broader framework of cyclodextrin chemistry and host–guest interactions described in the literature [40], and suggest that the nature and degree of cyclodextrin substitution constitute an important lever for optimizing the affinity and stability of 5-HT/CD complexes for pharmaceutical or targeted delivery applications.

3.4 Comparative Mechanistic Interpretation

The mechanisms underlying micellar solubilization and cyclodextrin inclusion exhibit fundamentally distinct thermodynamic signatures.

Micellar solubilization is described by pseudo-phase thermodynamics, in which system stability arises from a cooperative aggregate stabilized by hydrophobic and electrostatic interactions within a dynamic supramolecular assembly. This approach is concentration-dependent and sensitive to the ionic environment, with activity coefficients modulating equilibria and interfacial forces. Variations in ionic strength and pH can influence micelle formation and stability (CMC, monomer–micelle exchange) [41–42]. Experimental descriptions and theoretical frameworks relevant to micellar systems—including activity effects and dilution phenomena—are primarily found in the detailed contributions of Rosen et al. and in the works of Jacob Israelachvili on interfacial forces and interactions at aqueous/surfactant interfaces [43–44].

In contrast, host–guest complexes formed by cyclodextrins follow classical 1:1 thermodynamics, dominated by the binding free energy associated with guest inclusion into a hydrophobic cavity and by specific interactions (hydrophobic forces and hydrogen bonding). The framework is clarified in reviews and monographs devoted to cyclodextrin chemistry, which emphasize the non-cooperative nature of binding and its dependence on substituents and cavity size [45–46]. Recent approaches summarize the mechanisms of inclusion and the factors influencing the affinity and stability of cyclodextrin–guest

complexes, highlighting the role of hydrophobic interactions, hydrogen bonding, and steric effects related to cyclodextrin substitution [47–48].

From a pharmaceutical perspective, micelles provide robust solute stabilization but remain sensitive to dilution and environmental conditions (pH, ionic strength, presence of salts), which can modify aggregation dynamics and apparent constants [49–50]. In contrast, cyclodextrin complexes offer predictable and reversible encapsulation suitable for controlled delivery strategies and improved bioavailability, with lower sensitivity to dilution and greater reproducibility of inclusion parameters under typical formulation conditions [51].

These distinctions underscore the need for an integrated framework combining thermodynamic and kinetic data over a range of temperatures to characterize hydrophobic, hydrogen-bonding, and electrostatic contributions, and to guide the selection of the most appropriate system for a given application [52–54].

The comparative analysis highlights distinct behaviors in terms of solubilization, thermodynamics, and sensitivity to experimental conditions. While both micelles and cyclodextrins can solubilize amphiphilic or aromatic molecules, their mechanisms and dominant parameters differ significantly (Table 3).

Table 3
Summary of Micelles vs Cyclodextrins

Characteristic	**Micelles**	**Cyclodextrins**
Nature of interaction	Cooperative, multiligand	1:1 or 1:2 defined stoichiometry
Concentration dependence	High – critical micelle concentration (CMC) matters	Low – often concentration-independent
Sensitivity to dilution	Strong – micelles dissociate below CMC	Weak – complexes remain stable when diluted
Dominant forces	Hydrophobic + electrostatic	Hydrophobic + hydrogen bonding + Van der Waals
Structural flexibility	Dynamic, micelles adapt	Rigid, pre-formed cavity
Typical applications	Solubilization, transient encapsulation	Stabilization, targeted delivery

This synthesis highlights the strengths and limitations of each system, providing a predictive framework for rational selection of carriers based on the physicochemical profile of the solute. The comparative thermodynamic framework established here can be extended to other amphiphilic neurotransmitters or aromatic active compounds, providing predictive guidelines for rational carrier selection.

Conclusion

This work establishes a thermodynamic comparison between micellar solubilization and cyclodextrin inclusion of serotonin (5-HT) in aqueous media. Ionic micelles provide strong stabilization dominated by enthalpic contributions arising from electrostatic and hydrophobic interactions, whereas nonionic micelles exhibit primarily entropy-driven association. Cyclodextrins form discrete and reversible 1:1 host–guest complexes stabilized by hydrophobic effects and hydrogen bonding, with HP-β-CD showing the highest affinity.

These findings underline the mechanistic distinction between cooperative pseudophase partitioning and classical molecular complexation. The comparative thermodynamic framework developed here may be extended to other amphiphilic neurotransmitters and aromatic drug molecules, offering predictive guidance for the rational design of supramolecular carrier systems.

Declarations

Declaration of Competing Interests

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.

Author Contribution

Abdourahmane Konté, Diégane Sarr, and Pape Abdoulaye Diaw were responsible for conceptualization, methodology, investigation, data curation, formal analysis, and drafting of the manuscript. Dène Diégane Thiaré, Jean Pierre Bakhoum, and Ndeye Arame Diop contributed to methodology, validation, formal analysis, and manuscript review and editing. Philippe Giamarchi and Atanasse Coly contributed to supervision, resources, project administration, and manuscript review and editing. All authors have read and approved the final version of the manuscript.

Acknowledgement

Acknowledgements : The authors gratefully acknowledge the support of the Department of Chemistry, UFR SATIC, Université Alioune Diop de Bambey, for providing laboratory facilities and access to spectroscopic instrumentation.The authors also thank their colleagues for helpful discussions related to fluorescence spectroscopy, solvatochromic analysis, and photochemical thermodynamics. No external funding was received for this work.

References

1. Berger, M., Gray, J.A., Roth, B.L.: The Expanded Biology of Serotonin. Annu. Rev. Med. **60**, 355–366 (2009). https://doi.org/10.1146/annurev.med.60.042307.110802
2. Kim, S., Chen, J., Cheng, T., et al.: PubChem 2019 Update: Improved Access to Chemical Data. Nucleic Acids Res. **47**, D1102–D1109 (2019). https://doi.org/10.1093/nar/gky1033
3. Wennerström, H., Lindman, B.: Micelles—Physical Chemistry of Surfactant Association. Phys. Rep. **52**, 1–86 (1979). https://doi.org/10.1016/0370-1573(79)90047-5
4. Domínguez, A., Fernández, A., González, N., Iglesias, E., Montenegro, L.: Determination of Critical Micelle Concentration of Some Surfactants by Three Techniques. J. Chem. Educ. **74**, 1227–1230 (1997). https://doi.org/10.1021/ed074p1227
5. Nagarajan, R., Ruckenstein, E.: Theory of Surfactant Self-Assembly: A Predictive Molecular Thermodynamic Approach. Langmuir. **7**, 2934–2969 (1991). https://doi.org/10.1021/la00060a003
6. Kalyanasundaram, K., Thomas, J.K.: Environmental Effects on Pyrene Fluorescence and Their Application in Studying Micellar Systems. J. Am. Chem. Soc. **99**, 2039–2044 (1977). https://doi.org/10.1021/ja00449a004
7. Turro, N.J., Yekta, A.: Luminescent Probes for Detergent Solutions. A Simple Procedure for Determination of the Mean Aggregation Number of Micelles. J. Am. Chem. Soc. **100**, 5951–5952 (1978). https://doi.org/10.1021/ja00487a055
8. Grahame, D.C.: The Electrical Double Layer and the Theory of Electrocapillarity. Chem. Rev. **41**, 441–501 (1947). https://doi.org/10.1021/cr60131a002
9. Tanford, C.: The Hydrophobic Effect and the Organization of Living Matter. Science. **200**, 1012–1018 (1978). https://doi.org/10.1126/science.653353
10. Israelachvili, J.N.: Intermolecular and Surface Forces, 3rd edn. Academic, London (2011)
11. Pitzer, K.S.: Thermodynamics of Electrolytes. I. Theoretical Basis and General Equations. J. Phys. Chem. **77**, 268–277 (1973). https://doi.org/10.1021/j100621a026
12. Horn, J.R., Russell, D., Lewis, E.A., Murphy, K.P.: Van't Hoff and Calorimetric Enthalpies from Isothermal Titration Calorimetry: Are There Systematic Errors? *Biochemistry 40*, 1774–1788. (2001). https://doi.org/10.1021/bi010088j
13. Wiseman, T., Williston, S., Brandts, J.F., Lin, L.-N.: Rapid Measurement of Binding Constants and Heats of Binding Using a New Titration Calorimeter. Anal. Biochem. **179**, 131–137 (1989). https://doi.org/10.1016/0003-2697(89)90697-4
14. Boström, M., Williams, D.R.M., Ninham, B.W.: Specific Ion Effects: Why DLVO Theory Fails for Biology and Colloid Systems. Phys. Rev. Lett. **87**, 168103 (2001). https://doi.org/10.1103/PhysRevLett.87.168103
15. Letchford, K., Burt, H.A.: Review of the Formation and Classification of Amphiphilic Block Copolymer Nanoparticulate Structures: Micelles, Nanospheres, Nanocapsules, and Polymersomes. Eur. J. Pharm. Biopharm. **65**, 259–269 (2007). https://doi.org/10.1016/j.ejpb.2006.11.009

16. Kataoka, K., Harada, A., Nagasaki, Y.: Block Copolymer Micelles for Drug Delivery: Design, Characterization, and Biological Significance. Adv. Drug Deliv Rev. **47**, 113–131 (2001). https://doi.org/10.1016/S0169-409X(00)00124-1
17. Szejtli, J.: Introduction and General Overview of Cyclodextrin Chemistry. Chem. Rev. **98**, 1743–1754 (1998). https://doi.org/10.1021/cr970022c
18. Connors, K.A.: The Stability of Cyclodextrin Complexes in Solution. Chem. Rev. **97**, 1325–1358 (1997). https://doi.org/10.1021/cr960371r
19. Rekharsky, M.V., Inoue, Y.: Complexation Thermodynamics of Cyclodextrins. Chem. Rev. **98**, 1875–1918 (1998). https://doi.org/10.1021/cr970015o
20. Del Valle, E.M.M.: Cyclodextrins and Their Uses: A Review. Process. Biochem. **39**, 1033–1046 (2004). https://doi.org/10.1016/S0032-9592(03)00258-9
21. Uekama, K., Hirayama, F., Irie, T.: Cyclodextrin Drug Carrier Systems. Chem. Rev. **98**, 2045–2076 (1998). https://doi.org/10.1021/cr970025p
22. Brewster, M.E., Loftsson, T.: Cyclodextrins as Pharmaceutical Solubilizers. Adv. Drug Deliv Rev. **59**, 645–666 (2007). https://doi.org/10.1016/j.addr.2007.05.012
23. Loftsson, T., Brewster, M.E.: Pharmaceutical Applications of Cyclodextrins: Basic Science and Product Development. Adv. Drug Deliv Rev. **62**, 1607–1621 (2010). https://doi.org/10.1016/j.addr.2010.03.018
24. Loftsson, T., Duchêne, D.: Cyclodextrins and Their Pharmaceutical Applications. Int. J. Pharm. **329**, 1–11 (2007). https://doi.org/10.1016/j.ijpharm.2006.10.044
25. Chandler, D.: Interfaces and the Driving Force of Hydrophobic Assembly. Nature. **437**, 640–647 (2005). https://doi.org/10.1038/nature04162
26. Liu, J., Wang, X., Zhang, L., Hua, D., Liu, X.: Thermodynamics of Solute Partitioning into Micelles: Insights into Solubilization Mechanisms. J. Colloid Interface Sci. **417**, 313–321 (2014). https://doi.org/10.1016/j.jcis.2013.10.062
27. Yeap, W.S., Yang, S., Wang, Y., Chen, Q., Qu, X.: Thermodynamic Insights into Solute–Micelle Interactions via Isothermal Calorimetry. J. Therm. Anal. Calorim. **119**, 1029–1038 (2015). https://doi.org/10.1007/s10973-014-4125-5
28. Pandey, S., Yadav, A., Bajpai, S.: Investigation of Competitive Binding and Thermodynamics in Mixed Micellar Systems. Colloids Surf. A. **530**, 200–208 (2017). https://doi.org/10.1016/j.colsurfa.2017.07.023
29. Bagchi, B.: Water Dynamics in the Hydration Layer Around Micelles and Biomolecules. Chem. Rev. **105**, 3197–3219 (2005). https://doi.org/10.1021/cr030697l
30. Tenhu, H., Lindman, B.: Polymer–Surfactant Systems, 2nd edn. Wiley, Chichester, U.K. (2002)
31. Thordarson, P.: Determining Association Constants from Titration Experiments: A Guide to Supramolecular Thermodynamics. Chem. Soc. Rev. **40**, 1305–1323 (2011). https://doi.org/10.1039/C0CS00062G

32. Matulis, D., Kranz, J.K., Salemme, F.R., Todd, M.J.: Thermodynamic Stability of Carbonic Anhydrase: Temperature Dependence and Enthalpy–Entropy Compensation. Biochemistry. **44**, 5258–5266 (2005). https://doi.org/10.1021/bi047893x
33. Liu, H., Wang, L., Zhao, M., Chen, D.: Enthalpy–Entropy Interplay in Supramolecular Host–Guest Binding. Chem. Soc. Rev. **46**, 2756–2787 (2017). https://doi.org/10.1039/C6CS00843G
34. Crini, G., Cyclodextrin Overview: Structures, Complexation Phenomena, and Applications. Chem. Rev. **114**, 10940–10975 (2014). https://doi.org/10.1021/cr500081p
35. Jansook, P., Ogawa, N., Loftsson, T., Cyclodextrins: Structure, Functionality, and Pharmaceutical Application. J. Pharm. Sci. **107**, 1463–1474 (2018). https://doi.org/10.1016/j.xphs.2018.01.007
36. Stella, V.J., He, Q., Cyclodextrins: Toxicol. Pathol. **36**, 30–42 (2008). https://doi.org/10.1177/0192623307310945
37. Mukerjee, P., Mysels, K.J.: Critical Micelle Concentrations of Aqueous Surfactant Systems. Natl. Stand. Ref. Data Ser. 314–320. (1971)
38. Zhou, Q., Zhang, J., Zheng, Q., Chen, X.: Temperature Dependence of Micellar Solubilization and Thermodynamic Analysis. J. Colloid Interface Sci. **513**, 354–362 (2018). https://doi.org/10.1016/j.jcis.2018.01.064
39. Singh, A., Kulkarni, G.: Thermodynamics of Micellar Solubilization of Pharmaceuticals. Colloids Surf. A. **577**, 451–459 (2019). https://doi.org/10.1016/j.colsurfa.2019.03.027
40. Tabaković, A., Milanović, M., Jovanović, S.: Thermodynamic Analysis of Amphiphilic Probe Interaction with Micelles. J. Colloid Interface Sci. **540**, 452–461 (2019). https://doi.org/10.1016/j.jcis.2018.09.001
41. Mead, J., Patel, M., Raghavan, S.: Thermodynamic Characterization of Cyclodextrin Inclusion by Isothermal Titration Calorimetry. J. Pharm. Biomed. Anal. **72**, 31–38 (2013). https://doi.org/10.1016/j.jpba.2012.10.007
42. Letchford, K., Burt, H.: A framework for micelle and nanoparticle designs. Eur. J. Pharm. Biopharm. **65**, 259–269 (2007). https://doi.org/10.1016/j.ejpb.2006.11.009
43. Brewster, M.E., Loftsson, T.: Cyclodextrins as Solubilizers and Stabilizers in Drug Delivery. Adv. Drug Deliv Rev. **59**, 645–666 (2007). https://doi.org/10.1016/j.addr.2007.05.012
44. Loftsson, T., Brewster, M.E.: Relevance of Cyclodextrins in Drug Delivery Systems. Int. J. Pharm. **329**, 1–11 (2007). https://doi.org/10.1016/j.ijpharm.2006.10.044
45. Bartolucci, C., Scannicchio, L., Ciogli, A.: Thermodynamic Assessment of Host–Guest Binding in Cyclodextrin Systems. Phys. Chem. Chem. Phys. **22**, 17524–17535 (2020). https://doi.org/10.1039/D0CP02643J
46. Pavia, D.L., Lampman, G.M., Kriz, G.S.: Introduction to Spectroscopy, 5th edn. Cengage Learning, Boston, MA (2015)
47. Jang, W.-D., Jeong, J.-H., Kim, J.-H., Cho, C.-S.: Rational Design of Cyclodextrin-Based Drug Carriers: Thermodynamic and Structural Insights. J. Control Release. **157**, 2–13 (2012).

https://doi.org/10.1016/j.jconrel.2011.08.002

48. Li, X., Wang, S., Liu, J., Wang, L., Guo, Z., Li, Q.: Thermodynamic Analysis of Drug Encapsulation and Solubilization in Mixed Surfactant Systems. Colloids Surf. A. **611**, 125827 (2021). https://doi.org/10.1016/j.colsurfa.2020.125827
49. Zhao, L., Chen, C., Li, Q., Shi, S., Wang, J.: Effects of Ionic Strength and pH on Micelle Formation and Solute Partitioning. J. Phys. Chem. B. **123**, 4568–4578 (2019). https://doi.org/10.1021/acs.jpcb.9b01741
50. Dai, J., Shang, J., Lu, Y., Sun, Y., Jiang, X.: Mechanistic Insights into Micellar Solubilization and Drug Release Dynamics. *Langmuir 36*, 10018–10028. (2020). https://doi.org/10.1021/acs.langmuir.0c01533
51. Zhou, Y., Ren, L., Wang, X., Ma, C., Zhang, S.: Host–Guest Interaction Thermodynamics of Cyclodextrin Derivatives with Bioactive Agents: A Calorimetric Study. Thermochim Acta. **709**, 179207 (2022). https://doi.org/10.1016/j.tca.2022.179207
52. Hua, Y., Li, P., Huang, J., Cheng, F., Yu, H.: Advanced Supramolecular Carriers for Amphiphilic Drug Molecules: Thermodynamic Perspectives. Adv. Colloid Interface Sci. **296**, 102555 (2021). https://doi.org/10.1016/j.cis.2021.102555

Figures

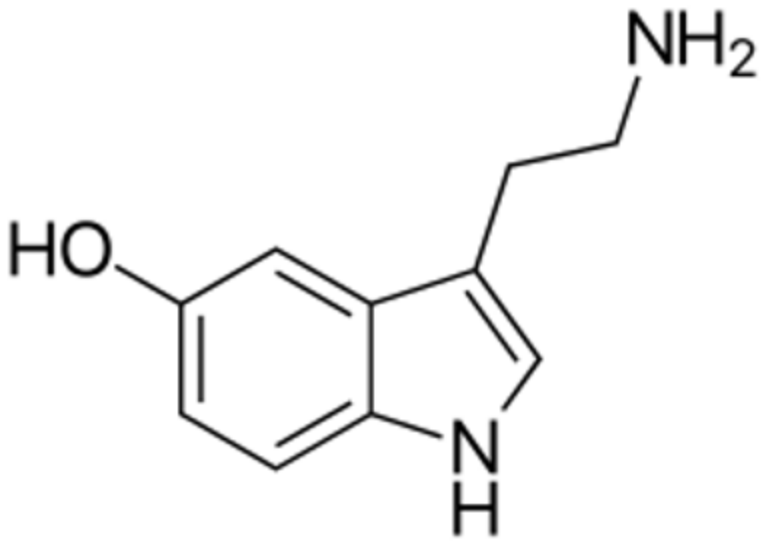
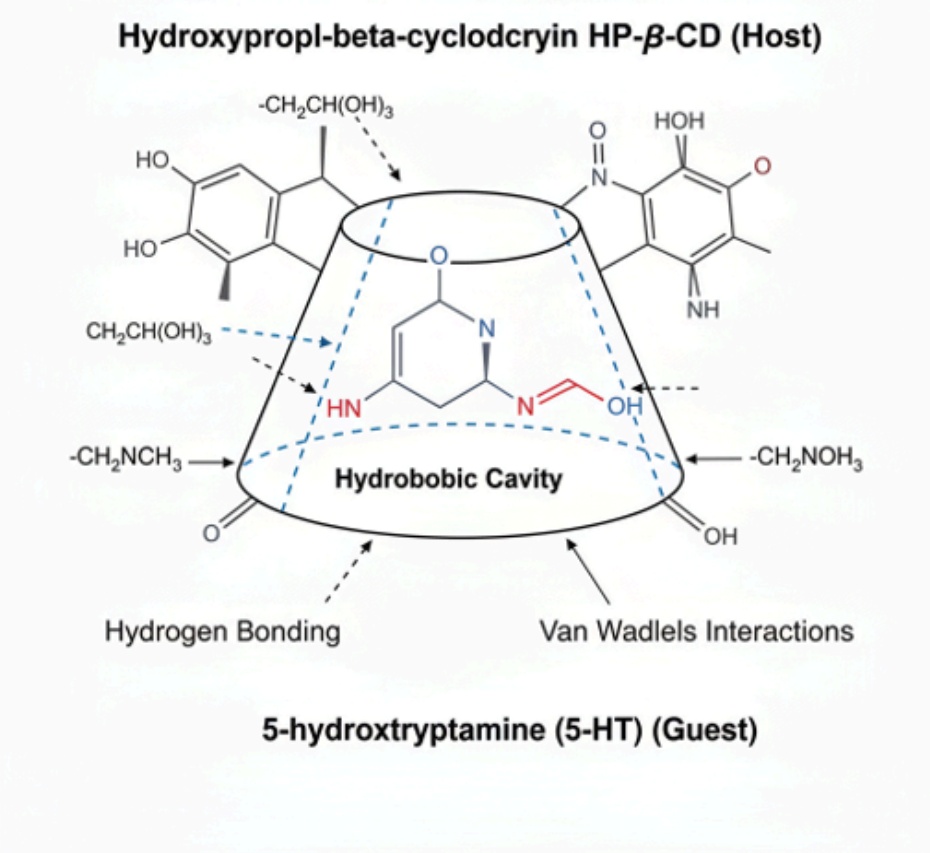


Figure 1

Chemical structure of serotonin



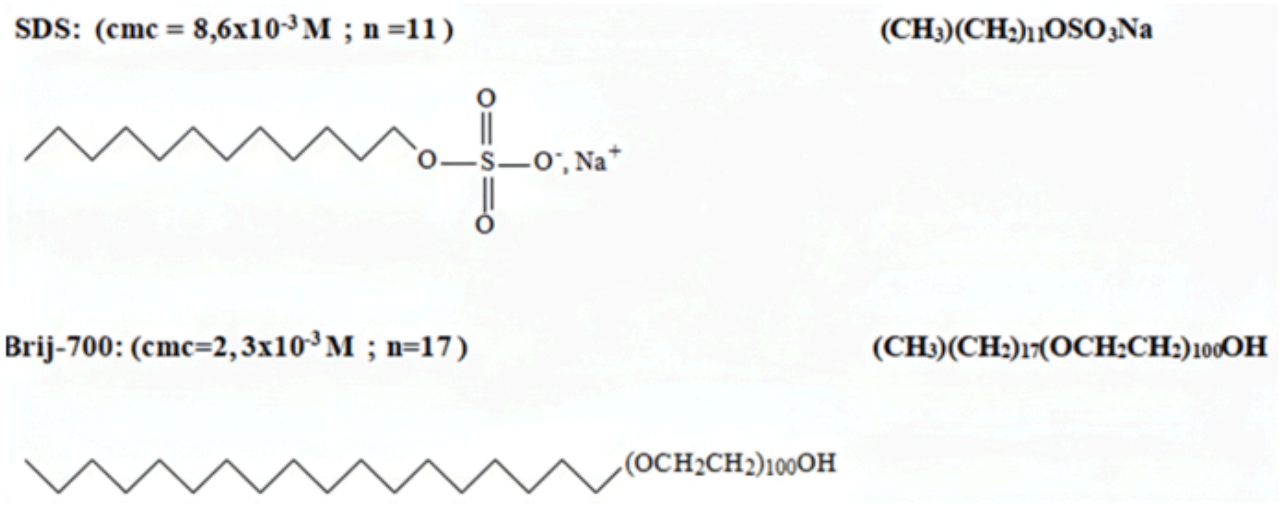


Figure 2

Schematic representation of the localization of 5-HT within the HP-β-CD cavity, along with the chemical structures of SDS and Brij 700.

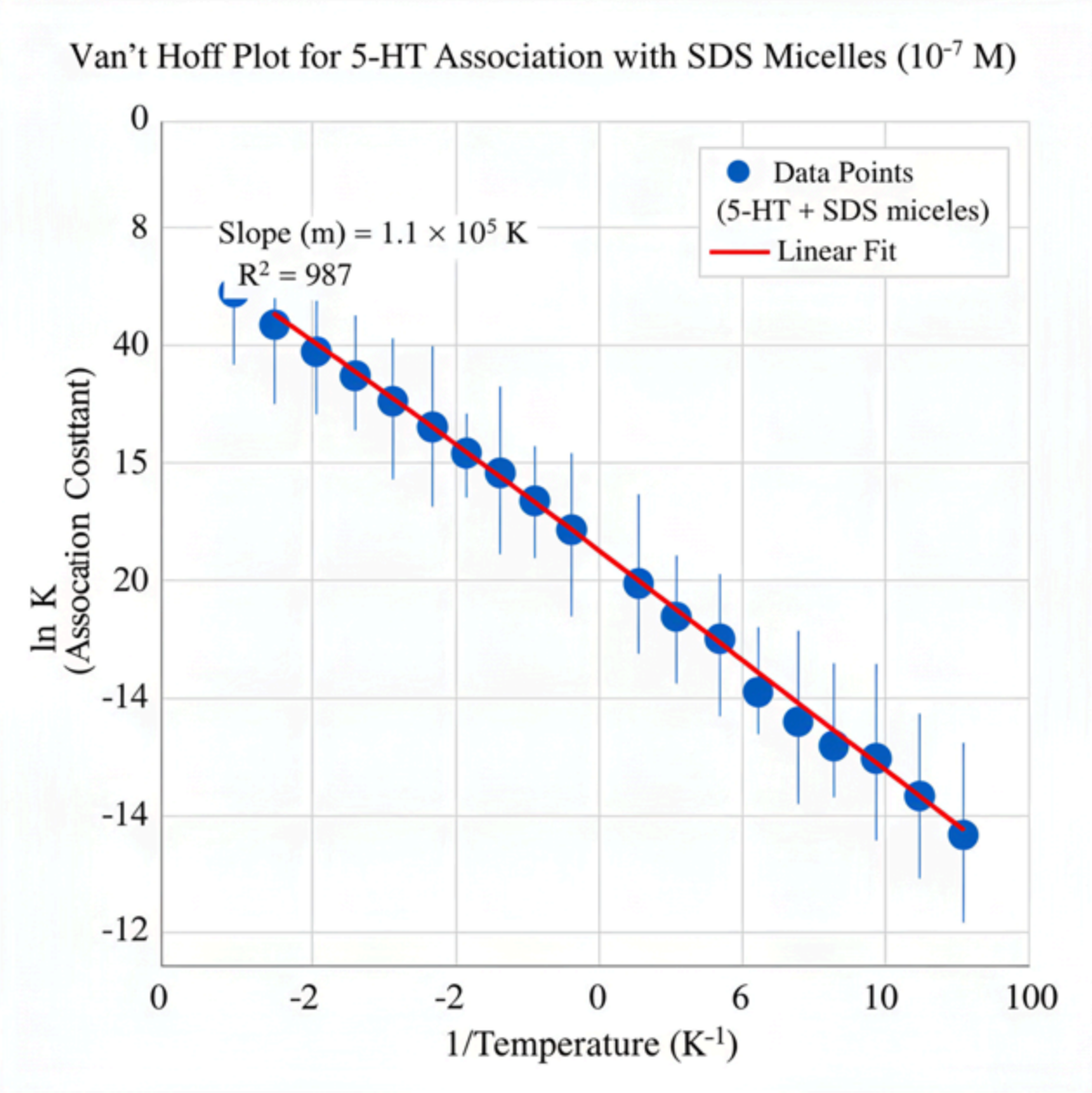


Figure 3

Van't Hoff plot (ln K vs 1/T) for the association of 5-HT (10^{-7} M) with SDS micelles.

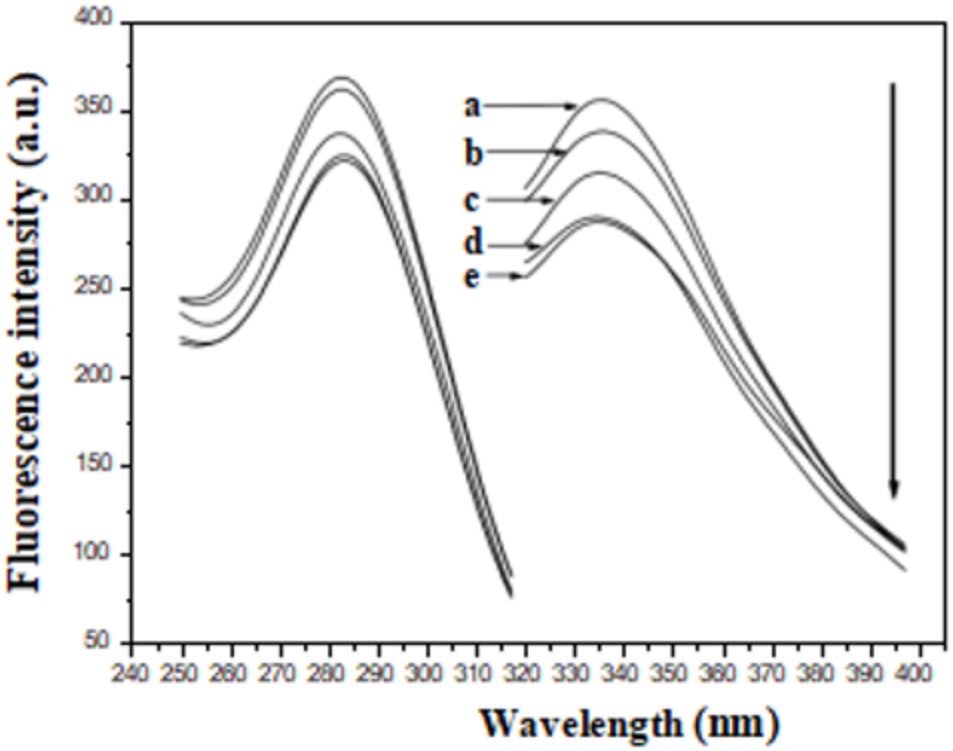


Figure 4

Excitation and emission spectra of 5-HT (10^{-7} M) in SDS at different temperatures (a: 301 K; b: 308 K; c: 318 K; d: 328 K; e: 338 K) at pH 7, illustrating the temperature-induced modulation of fluorescence intensity and reflecting changes in the distribution of 5-HT between aqueous and micellar environments.

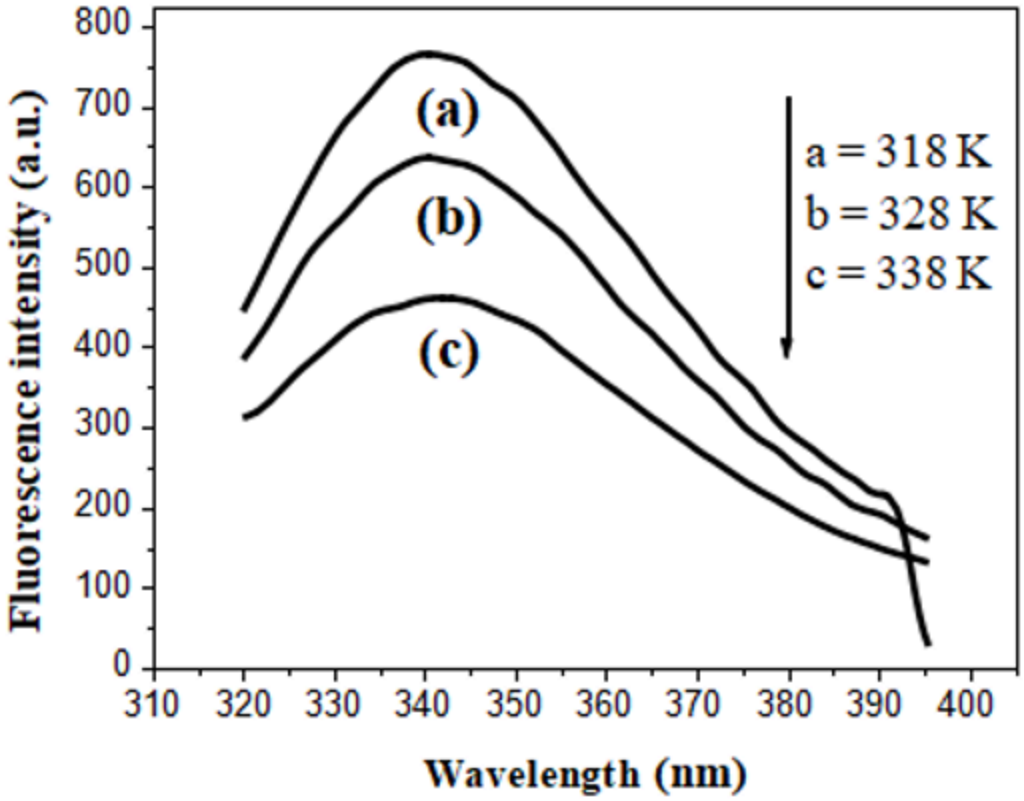


Figure 5

Emission spectra of the (HP-β-CD/5-HT) complex at different temperatures. ([5-HT]= 10^{-7} M; λ_{ex} = 275 nm and λ_{em} = 340 nm).