ISABELA ARAUJO MARQUES

TERMODINÂMICA DE FORMAÇÃO DE COMPLEXOS SUPRAMOLECULARES ENTRE β-CICLODEXTRINA E SURFACTANTES NÃO IÔNICOS BRIJ

Dissertação apresentada à Universidade Federal de Viçosa, como parte das exigências do Programa de Pós-Graduação em Agroquímica, para obtenção do título de *Magister Scientiae*.

Orientador: Luis Henrique Mendes da Silva

Coorientadora: Ana Clarissa dos Santos Pires

VIÇOSA – MINAS GERAIS
2020

Ficha catalográfica elaborada pela Biblioteca Central da Universidade Federal de Viçosa - Campus Viçosa

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M357t
2020

Marques, Isabela Araujo, 1995-
Termodinâmica de formação de complexos supramoleculares entre ?-ciclodextrina e surfactantes não iônicos Brij / Isabela Araujo Marques. – Viçosa, MG, 2020.
69 f.: il. (algumas color.).

Inclui apêndice.
Orientador: Luis Henrique Mendes da Silva.
Dissertação (mestrado) - Universidade Federal de Viçosa, Departamento de Química, 2020.
Inclui bibliografia.

1. Química supramolecular. 2. Ciclodextrinas. 3. Agentes ativos de superfície. 4. Calorimetria. 5. Líquidos iônicos. I. Silva, Luis Henrique Mendes da, 1967-. II. Universidade Federal de Viçosa. Departamento de Química. Programa de Pós-Graduação em Agroquímica. III. Título.

CDD 22. ed. 547.7

Bibliotecário(a) responsável: Alice Regina Pinto Pires CRB-6/2523

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APROVADA: 18 de fevereiro de 2020

Assentimento:

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Isabela Araujo Marques
Autora

_____

Luis Henrique Mendes da Silva
Orientador

AGRADECIMENTOS

À minha família, Cleide, Evaldo e Guilherme, pelo apoio e por possibilitar essa conquista.

Aos meus amigos, Kamila, César e Joanna, que me acompanharam durante toda essa jornada e que, sem eles, todo esse processo não teria valido a pena.

A Yara e Álvaro que, além do apoio, incentivo e contribuição para o meu desenvolvimento, se tornaram amigos valiosos que levarei para vida.

Aos demais colegas e amigos que fiz durante os anos em Viçosa.

Ao professor Luis Henrique por todo aprendizado, orientação e pela oportunidade de desenvolver esse trabalho.

Aos membros dos grupos pesquisa QUIVECOM e THERMA pela ajuda disponibilizada.

Às professoras Ana Clarissa e Márcia por aceitarem participar da banca da defesa.

À Universidade Federal de Viçosa, por todo conhecimento adquirido e pelos momentos especiais proporcionados, que ficarão sempre em minha memória.

Às agências de fomento CNPq, FAPEMIG e CAPES pelo apoio financeiro.

“I understand now that boundaries between noise and sound are conventions. All boundaries are conventions, waiting to be transcended. One may transcend any convention, if only one can first conceive of doing so.” (Cloud Atlas, 2013)

RESUMO

MARQUES, Isabela Araujo, M.Sc., Universidade Federal de Viçosa, fevereiro de 2020. **Termodinâmica de formação de complexos supramoleculares entre β-ciclodextrina e surfactantes não iônicos Brij**. Orientador: Luis Henrique Mendes da Silva. Coorientadora: Ana Clarissa dos Santos Pires.

Desde o estabelecimento da química supramolecular como uma nova área científica, ela vem sendo alvo constante de pesquisa, por contribuir para o desenvolvimento de novas tecnologias. Um tipo de sistema supramolecular particularmente interessante é o dos complexos hóspede-hospedeiro, que consistem de estruturas formadas pela interação entre molécula-molécula ou molécula-íon. A partir dessa interação, as propriedades das moléculas/íons interagentes podem ser modificadas ou até mesmo novas funcionalidades podem ser geradas, o que torna o estudo desses complexos interessantes para aplicações industriais. Entretanto, para utilizar essas supramoléculas da melhor forma possível, é necessário compreender como elas se formam e como suas propriedades podem ser moduladas, o que é realizado a partir de estudos termodinâmicos. Tendo isso em mente, nesta dissertação objetivou-se realizar a caracterização termodinâmica, por meio da técnica de calorimetria de titulação isotérmica, da formação de complexos hóspede-hospedeiro entre β-ciclodextrina e quatro surfactantes não-iônicos Brij. O sistema ciclodextrina-surfactante foi particularmente escolhido uma vez que ao variar a estrutura do surfactante (o tamanho da cauda e do grupo cabeça) é possível compreender como a hidrofobicidade/hidrofilicidade da molécula hóspede afeta a formação do complexo. Além disso, apesar da β-ciclodextrina ser comumente utilizada no estudo de formação de complexos hóspede-hospedeiros, devido a seu baixo custo e capacidade de incluir uma grande variedade de moléculas e íons, a interação dessa molécula macrocíclica com os surfactantes Brij foi pouco explorada termodinamicamente. Assim, os resultados obtidos mostraram que a β-ciclodextrina interage tanto com a cauda quanto com o grupo cabeça dos surfactantes e que a estabilidade dos complexos depende do tamanho de ambas as partes. A interação foi entalpicamente dirigida, para todos os surfactantes, devido, principalmente, à dessolvatação da cavidade da β-ciclodextrina, à formação de novas interações entre as moléculas hóspede e hospedeira e às mudanças conformacionais sofridas pelos surfactantes. Entretanto, para os Brijs com a cauda mais longa, os complexos formados se agregaram em grandes estruturas, sendo essa agregação promovida ainda mais pela presença de diferentes concentrações do líquido iônico 1-butil-3-metilimidazolium no sistema. Esses resultados mostram que, apesar da grande quantidade de

estudos envolvendo a formação de complexos hóspede-hospedeiro, presentes na literatura científica, informações importantes ainda podem ser extraídas desses sistemas.

Palavras-chave: Química supramolecular. Complexo hóspede-hospedeiro. Ciclodextrinas. Surfactante não-iônico. Calorimetria de titulação isotérmica. Líquido iônico.

ABSTRACT

MARQUES, Isabela Araujo, M.Sc., Universidade Federal de Viçosa, February, 2020. **Thermodynamics of supramolecular complexes formation between β-cyclodextrin and nonionic surfactants Brij**. Adviser: Luis Henrique Mendes da Silva. Co-adviser: Ana Clarissa dos Santos Pires.

Since the establishment of supramolecular chemistry as a scientific field, it has been a constant target of research for contributing to the development of new technologies. A type of supramolecular system particularly interesting is the host-guest complexes, which consist of structures formed by the interaction between molecule-molecule or molecule-ion. Through this interaction, the properties of the interacting molecules/ions can be modified or even new ones can be created, which makes the study of such complexes interesting for industrial applications. However, to use these supramolecules in the best way possible, it is necessary to comprehend how they form and how their properties can be modulated, which is done through thermodynamic studies. With this in mind, this dissertation had as a goal the thermodynamic characterization, via the isothermal titration calorimetry technique, of the formation of host-guest complexes between β-cyclodextrin and four nonionic Brij surfactants. The cyclodextrin-surfactant system was particularly chosen because when the structure of the surfactants (the tail and head group length) is varied, as it was done here, it is possible to comprehend how the molecules' hydrophobicity/hydrophilicity affects the complex formation. Moreover, although β-cyclodextrin is commonly used for studying the formation of host-guest complexes, due to its low cost and capacity to include a great variety of molecules and ions, the interaction of this macrocyclic molecule with the Brij surfactants was little explored thermodynamically. Thus, the results obtained showed β-cyclodextrin interacts with both the surfactants' tail and head group and the stability of the complexes depended on the length of these moieties. The complex formation was enthalpy-driven for all surfactants due, mainly, to the desolvation of the β-cyclodextrin's cavity, the formation of new interactions between the host and guest molecules, and the conformational changes suffered by the surfactants. However, for the Brijs with a longer tail, the complexes formed aggregated into large structures, being this aggregation promoted even more by the presence of different concentrations of the ionic liquid 1-butyl-3-methylimidazolium in the system. These results showed that, despite the substantial amount of studies involving the formation of host-guest complexes in the scientific literature, important information can still be extracted from these systems.

Keywords: Supramolecular chemistry. Host-guest complex. Cyclodextrin. Nonionic surfactant. Isothermal titration calorimetry. Ionic liquid.

LISTA DE SÍMBOLOS E ABREVIAÇÕES

CAC: critical aggregation concentration;

CD: cyclodextrin;

CMC: critical micellar concentration;

Cur: curcumin;

DLS: dynamic light scattering;

EEC: enthalpy-entropy compensation;

G: guest;

H: host;

$\bar{H}_w^{bulk}$**:** partial molar enthalpy of water in the bulk;

$\bar{H}_w^{shell}$**:** partial molar enthalpy of water in the shell;

HG: host-guest;

HP-β-CD: hydroxypropyl-β-cyclodextrin;

ITC: isothermal titration calorimetry;

K: stepwise equilibrium, binding or association constant;

k_b**:** intrinsic or microscopic binding constant;

N: number of injections in the calorimetric experiment;

n: number of identical and independent binding sites;

n_b^G**:** number of moles of bounded guest;

n_b^H**:** number of moles of bounded host;

n_G**:** number of moles of guest;

n_H**:** number of moles of host;

n_t^H**:** total number of moles of host;

PEO: poly (ethylene oxide);

q: heat;

q_{dil}**:** dilution heat;

q_i: heat associated with the complex formation, at each injection;

q_{int}: interaction heat;

$Q_T(i)$: total heat accumulated after i injections;

$Q_T(i-1)$: total heat accumulated after $i-1$ injections;

Q_T: total heat accumulated after N injections;

R: universal gas constant;

$\bar{S}_w^{bulk}$: partial molar entropy of water in the bulk;

$\bar{S}_w^{shell}$: partial molar entropy of water in the shell;

SSIS: single set of identical sites;

T: temperature;

t: time;

V_c: sample cell's effective volume;

V_{inj}: injection volume;

αCD: α-cyclodextrin;

β: overall equilibrium, binding or association constant;

βCD: β-cyclodextrin;

$βCD_3$: β-cyclodextrin trimer;

γCD: γ-cyclodextrin;

$\Delta G°$: standard free Gibbs energy change;

$\Delta H°$: standard enthaply change;

$\Delta H_{desolv.}$: desolvation enthaply change;

ΔH_i: enthaply change per mole of guest, at each injection;

ΔP: power;

$\Delta S°$: standard entropy change;

$\Delta S_{desolv.}$: desolvation entropy change;

$\bar{\nu}$: binding parameter.

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INTRODUCTION

"Where nature finishes producing its own species, man begins using natural things and in harmony with this very nature, to create an infinity of species." (Leonardo da Vinci)

The study of supramolecular structures has been a constant research target since its establishment as a discipline in 1987, given the large number of areas covered by it (HUANG; ANSLYN, 2015), such as molecular machines (MAVROIDIS; DUBEY; YARMUSH, 2004), molecular sensors (JI et al., 2013), chemical catalysis (BROWN et al., 2015), and drug delivery (WEBBER; LANGER, 2017). Among the several systems that fit into this domain of chemistry, the host-guest complexes are one of the most interesting. These compounds are formed by the encapsulation of one molecule by another via molecular recognition and, through this process, the guest molecule may have its properties modified. The most common host used in these systems is cyclodextrins, which are cyclic oligosaccharides with a truncated cone shape. The ability of these compounds to form inclusion complexes comes from their hydrophobic cavity and hydrophilic exterior: while the cavity can interact with ions, polar and apolar molecules, the exterior interacts with the water molecules (in the case of aqueous solution). Therefore, properties, such as solubility, stability, volatility, and controlled release of guest molecules, can be modulated (DEL VALLE, 2004).

Although host-guest complexes based on polymers (RUSA; LUCA; TONELLI, 2001), dyes (SZEJTLI, 2003), and drugs (LAZA-KNOERR; GREF; COUVREUR, 2010) show many applications in the food, textile, and pharmaceutical industries, the use of surfactants as a guest is especially intriguing. It is well known that cyclodextrins can prevent the formation of micelles since the hydrophobic moiety of the surfactant is encapsulated. Thus, in the presence of cyclodextrins, the critical micelle concentration of some surfactants tends to increase (VALENTE; SÖDERMAN, 2014). Moreover, the amphiphilic feature of these molecules generates different contributions to the intermolecular forces responsible for the complex formation, such as the hydrophobic effect, that tends to isolate the tail from the aqueous environment, making the process of desolvation different for the tail and head group (VALENTE; SÖDERMAN, 2014). In this way, by studying these inclusion complexes, it is possible to investigate the balance between the hydrophobic and hydrophilic contributions to the complex formation.

Besides the chemical structure of the surfactant, other factors such as temperature, pH, and the presence of cosolutes can affect the formation of inclusion complexes. The investigation of the last, in particular, provides valuable information of how these supramolecular structures form, especially in an aqueous medium, since the presence of the cosolute molecules can affect the water tridimensional network, consequently, altering the interaction between water and the host and/or guest molecules, as well as the interaction between the last two (HARRIES; RAU; PARSEGIAN, 2005). Studies of how some cosolutes, such as urea (SOUZA; ALVAREZ; POLITI, 2011), organic and inorganic salts (LO NOSTRO et al., 2006), affect supramolecular systems, have been reported over the years. However, a class of modern salts that have been catching the attention of the scientific community is the ionic liquids. These compounds, that can be found as molten salts at temperatures lower than the water boiling point, have as main properties the low vapor pressure and non-flammability, which made them great candidates to substitute organic solvents in different processes (FORSYTH; PRINGLE; MACFARLANE, 2004). Moreover, the great solvation ability of the ionic liquids make interesting their use as cosolutes in systems containing host-guest complexes, since they can modify the 3D water structure (AGUDELO et al., 2019), or even form inclusion complexes with the host, impairing the interaction with the guest molecule (TRAN; DE PAOLI LACERDA, 2002).

Given the number of valuable and interesting information the interaction between cyclodextrins and surfactants provides about the formation of host-guest complexes, this dissertation had as goal the investigation of the thermodynamics of interaction between several nonionic Brij surfactants and β-cyclodextrin, in water and aqueous solutions of the ionic liquid 1-butyl-3-methylimidazolium chloride, using the isothermal titration calorimetry technique.

Thus, this dissertation was divided into two chapters, the first one presenting a literature review on some relevant topics for understanding the subject under study, and the second one showing the study itself, with the obtained results and the discussion of their meaning.

CHAPTER 1: Literature review

1 Supramolecular chemistry

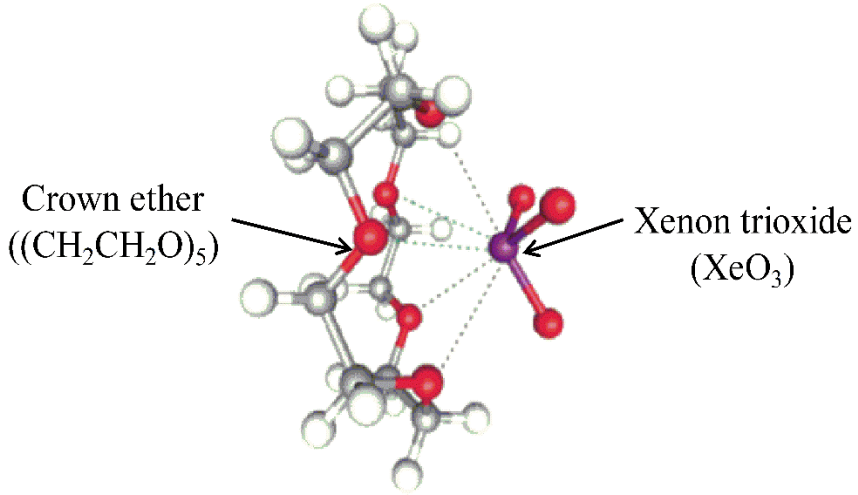
Supramolecular chemistry is defined as the “chemistry beyond the molecule”, being this concept presented by Jean-Marie Lehn, one of the founders of this domain (ARIGA; KUNITAKE, 2006). Although it seems a bit vague, this concept tells us the supramolecular chemistry is concerned with the study of structures formed by the association, through non-covalent interactions, of two or more molecules (or ions). Once the molecules interact to form different structures, named supramolecules, new properties can be acquired, which can be applicable in many scientific areas such as, biochemistry, molecular biology, nanotechnology, material science and so forth, making the supramolecular chemistry a multidisciplinary field.

Just as the number of molecules present in our world is immense, so is the quantity of supramolecules that can be obtained from them. To better comprehend how this myriad of structures form, and hence use them, it is imperative to take into account two important concepts, which can be considered as the basis for constructing supramolecules: molecular recognition and self-assembly phenomenon. In this way, the supramolecules can be divided into these two categories, in which the main differences between them are the size and shape of the structures, as will be explained below.

1.1 Host-guest complexes and molecular recognition

As mentioned, non-covalent intermolecular forces play a crucial role in the existence of supramolecules. In the case of the host-guest (HG) complexes, another factor is also essential for the formation of such structures, which is the selectivity. Basically, host-guest complexes are every structure formed by the interaction between a relatively small molecule or ion, named guest (G), and a larger one, named host (H), maintained together by intermolecular forces, as shown by the example in Fig. 1.1.

Fig. 1.1. Example of an HG complex formed by a crown ether (acting as host) and xenon trioxide (acting as guest).



Source: Adapted from MARCZENKO; MERCIER; SCHROBILGEN, 2018.

This interaction, however, is only possible if the host possesses a region (binding site) with the size, geometry, and functionalities capable of accommodating and binding the guest molecule (STEED; TURNER; WALLACE, 2007). In other words, the formation of the complex occurs via the molecular recognition of the guest by the host.

Examples of these complexes can be widely found in nature, where they participate in various processes that enable life, such as the interaction between protein and a variety of molecules (drugs, lipids, carbohydrates, etc.), recognition of a neurotransmitter by a receptor, and binding of a substrate to an enzyme. In fact, the concept of molecular recognition first appeared in the work of Emil Fisher, in 1894, when he observed that glycolytic enzymes could distinguish between the sugar stereoisomers. Based on this discovery, he proposed the binding of a substrate to an enzyme occurs through a lock and key model, in which the molecular recognition occurs due to the complementary geometry between the substrate and the enzyme's binding site (HOLYOAK, 2013). Although nowadays this lock and key model is no longer used, since more complete theories have been developed, such as the induced-fit, the findings of Emil Fisher were of great importance for the evolution of host-guest chemistry.

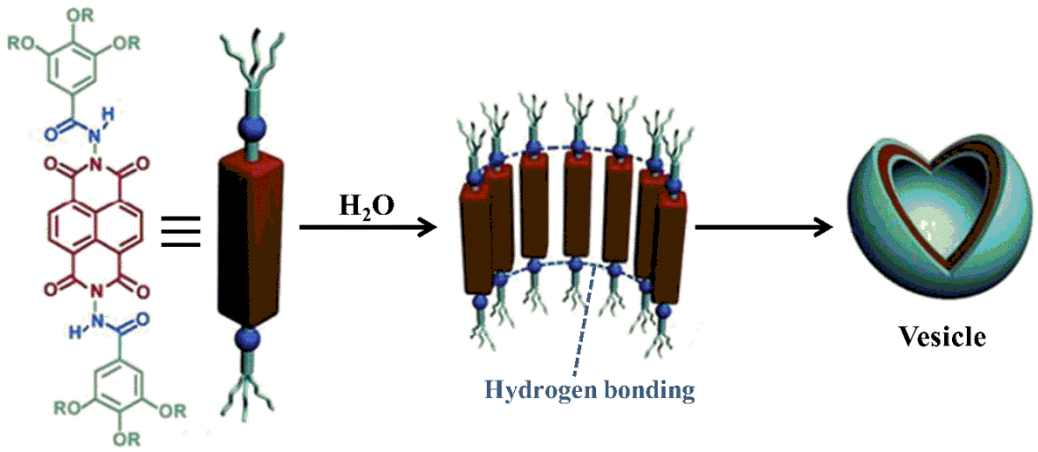
Over the years, the research on these area has been contributing for the discovery of a great variety of functionalities of these complexes, for instance, in controlled drug delivery (LIN et al., 2019), catalysis (DEMIR; BASCEKEN, 2013), molecular sensors (VÄLIMÄKI et al., 2018) and molecular machines (TAKASHIMA; HARADA, 2018). Thus, the extraordinary

potential of this field makes interesting the continuous investigation of different host-guest complexes, in pursuit of new functions.

1.2 Self-assembly phenomenon

The second category of supramolecules is the ones formed from the self-assembly phenomenon. These structures are constructed through the interaction between two or more molecules that do not differ significantly in size, yielding thermodynamically stable aggregates. (Fig. 1.2). And, while for the host-guest complexes the geometry of the structure is determined by the position of the functional groups of the interacting partners, the shape of the self-assembly supramolecules is dictated by the information contained in the molecular units (STEED; TURNER; WALLACE, 2007). Depending on this information and environmental conditions, structures with different sizes and shapes can be obtained, such as micelles, vesicles, bilayers, tubules and lamellae (SONG; SONG; HAO, 2014).

Fig. 1.2. Self-assembly structures formed by an amphiphilic molecule consisting of a central hydrophobic naphthalene-diimine attached to two hydrophilic moieties by a hydrazine group.

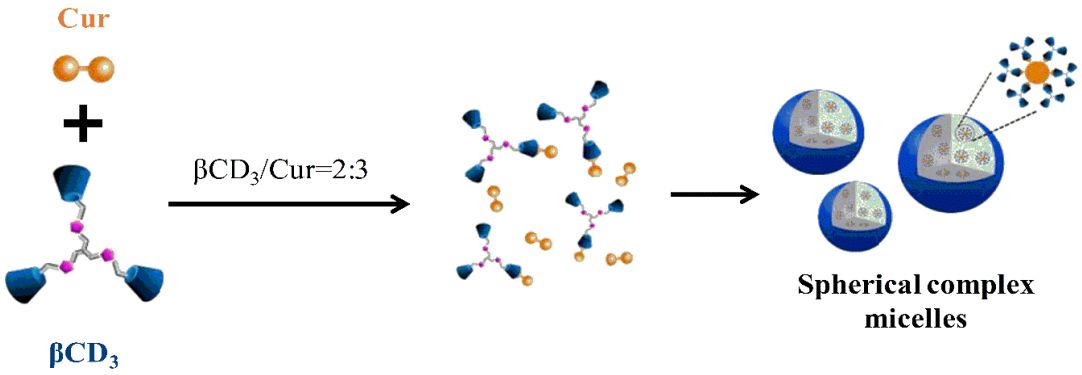


Source: Adapted from SIKDER; GHOSH, 2019.

In nature, the self-assembly phenomenon takes part in important processes such as the formation of the DNA double helix and the cell membranes, and the folding of proteins. Whereas for the applications, these supramolecules can be used as a carrier for other molecules (BHAT et al., 2017), as conjugates for antitumor therapy (ZOU et al., 2017), and for constructing nanotechnology (ZHOU et al., 2016).

Finally, although divided into two categories, the host-guest complexes and the self-assembly supramolecules can be combined, as shown in Fig. 2.3, where the host-guest complexes formed between a β-cyclodextrin trimer (βCD_3) and curcumin (Cur) self-assemble to form micelles, showing how versatile the supramolecular chemistry can be. However, to use these structures to their fullest potential, it is imperative to understand how they form and how their properties can be modulated, which is only possible through a thermodynamic study.

Fig. 1.3. Micelles based on βCD3-Cur host-guest complexes.



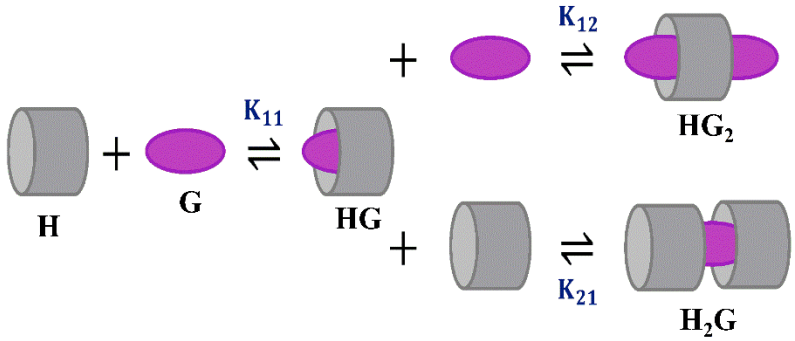
Source: Adapted from BAI et al., 2020.

2 Thermodynamics of host-guest complex formation

In this topic, the thermodynamics of host-guest complex formation will be discussed in detail, since this type of supramolecule was the main subject of the study performed in this dissertation. As for the thermodynamics involved in the self-assembly phenomenon, some key information will be presented later in section 4.

The thermodynamic analysis presented here was made considering the complexes are being formed in aqueous solution. In that way, since the formation of host-guest complex occur through non-covalent intermolecular forces, the process is reversible and involves an equilibrium between the free and complexed chemical species in solution, from which we can obtain an equilibrium constant, also known as binding or association constant, be the stepwise (K) or the overall (β), as shown in Scheme 1.1.

Scheme 1.1. Equilibrium between the host-guest complexes and the free species, along with the respective binding constants, where the terms in brackets represent the equilibrium concentration of each species.



Stepwise binding constants

$$K_{11} = \frac{[HG]}{[H][G]}$$

$$K_{21} = \frac{[H_2G]}{[HG][H]} \qquad K_{12} = \frac{[HG_2]}{[HG][G]}$$

$$\vdots$$

$$K_{m1} = \frac{[H_mG]}{[H_{m-1}G][H]} \qquad K_{1n} = \frac{[HG_n]}{[HG_{n-1}][G]}$$

Overall binding constants

$$mH + G \rightleftharpoons H_mG \qquad \beta_{m1} = K_{11} \times K_{21} \times \ldots \times K_{m1}$$

$$H + nG \rightleftharpoons HG_n \qquad \beta_{1n} = K_{11} \times K_{12} \times \ldots \times K_{1n}$$

$$mH + nG \rightleftharpoons H_xG_n \qquad \beta_{mn} = \frac{\beta_{m1} \times \beta_{1n}}{K_{11}}$$

Through the K (or β) values, the standard[1] Gibbs free energy change (ΔG°) can then be obtained from Eq. 1,

$$\Delta G^\circ = -RT \ln(K \text{ or } \beta) \qquad (1)$$

where R is the universal gas constant and T is the temperature. Like the equilibrium constant, ΔG° indicates the stability of the complexes formed. The greater the K (or β) value, more negative ΔG° becomes, which shows that, in the thermodynamic equilibrium, there are more HG complexes than the free species in solution. Moreover, the ΔG° value reflects the various processes occurring in the systems which lead to the HG complex formation. Among these processes, the most important ones are the **(i)** desolvation of the molecules, **(ii)** the interaction between them and, sometimes, **(iii)** the conformational changes suffered upon the interaction.

[1] The standard term indicates the thermodynamic parameter is related to the formation of 1 mol of HG complex under standard conditions of temperature and pressure (273.15 K and 1 bar).

To analyze each one of these processes, however, it is necessary to look at the standard enthalpy change ($\Delta H°$) and standard entropy change ($\Delta S°$), terms that contribute to the $\Delta G°$ values, as shown below.

$$\Delta G° = \Delta H° - T\Delta S° \quad (2)$$

Depending on the values of $\Delta H°$ and $\Delta S°$, the formation of HG complexes can be enthalpy-driven, when $\Delta H° < 0$ and $\Delta S° < 0$; entropy-driven, when $\Delta S° > 0$ and $\Delta H° > 0$; or both, when $\Delta H° < 0$ and $\Delta S° > 0$. To understand how each of these cases occurs, we need to analyze the three processes mentioned before:

(i) When a molecule or ion is in an aqueous solution, water molecules surround this chemical species, forming a solvation shell. Depending on the nature of this chemical species, the water molecules will be organized differently. For instance, water molecules solvating hydrophobic molecules tend to assume a highly structured network to maximize the hydrogen bonding between them, due to the unfavorable interaction with the hydrophobic molecule. Thus, when compared to the water molecules in the bulk[2], the partial molar enthalpy and entropy of the water in the solvation shell is lower ($\bar{H}_w^{shell} < \bar{H}_w^{bulk}$ and $\bar{S}_w^{shell} < \bar{S}_w^{bulk}$). Consequently, when the water molecules leave the solvation shell and go to the bulk, upon the interaction, there is an increase in the system's enthalpy and entropy, that is $\Delta H_{desolv.} = \bar{H}_w^{bulk} - \bar{H}_w^{shell} > 0$ and $\Delta S_{desolv.} = \bar{S}_w^{bulk} - \bar{S}_w^{shell} >$. However, there are cases that the water molecules solvating a hydrophobic region are less structured in the solvation shell than in the bulk, which is the case of the cyclodextrins (a common host used, that will be discussed in detail in section 3). Thus, in these cases $\Delta H_{desolv.} < 0$ and $\Delta S_{desolv.} < 0$.

(ii) The interaction between the H and G molecules occurs via non-covalent intermolecular forces which causes a decrease of the molecules' enthalpy, according to the energy necessary to maintain them together. This energy can range from 2 kJ mol^{-1} to 300 kJ mol^{-1}, depending on the type of interaction as shown in Table 1.1. Moreover, as the molecules interact, their free motion in solution is impaired,

[2] An isotropic region in the solution, where the solvent molecules are influenced only by themselves.

causing their degrees of freedom (translational, rotational and vibrational) to decrease, resulting also in a decrease of the molecules' entropy.

Table 1.1. Summary of supramolecular interactions.

Interaction	Energy (kJ mol^{-1})
Ion-ion	200-300
Ion-dipole	50-200
Dipole-dipole	5-50
Hydrogen bonding	4-120
Cation-π	5-80
π- π	0-50
van der Waals	< 5 (but variable depending on the surface area)

Source: Adapted from STEED; TURNER; WALLACE, 2007.

(iii) As for the conformational changes suffered by the molecules upon binding, the enthalpy and entropy changes will depend on the structure of the molecules that are interacting, assuming positive or negative values.

Therefore, for each HG complex, the three processes above will contribute in a different way, depending on the interacting partners. For instance, Cai et al. (2019) studied the formation of complexes between hydroxypropyl-β-cyclodextrin (HP-β-CD) and (E)-piceatannol, finding the process to be enthalpy-driven ($\Delta H° = -25.17$ kJ mol^{-1} and $T\Delta S° = -2.72$ kJ mol^{-1}), in water, due to the desolvation of the HP-β-CD's cavity and the interaction between the molecules through van der Waals and hydrogen bonding. While the binding of β-lapachone to β-cyclodextrin, studied by Xavier-Junior et al. (2017), was enthalpically and entropically favorable ($\Delta H° = -6.58$ kJ mol^{-1} and $T\Delta S° = 13.32$ kJ mol^{-1}), due to the molecules desolvation and formation of new interactions.

2.1 Determination of the thermodynamic parameters

A great variety of techniques can be used for determining the thermodynamic parameters related to the formation of HG complexes. The approach of each technique can be divided into two: (I) the direct measurement of the equilibrium concentration of free and bound molecules using equilibrium dialysis (PRADO et al., 2017), which allows the calculation of the binding constants, as shown in Scheme 1.1; and (II) the measurement of a physical observable that

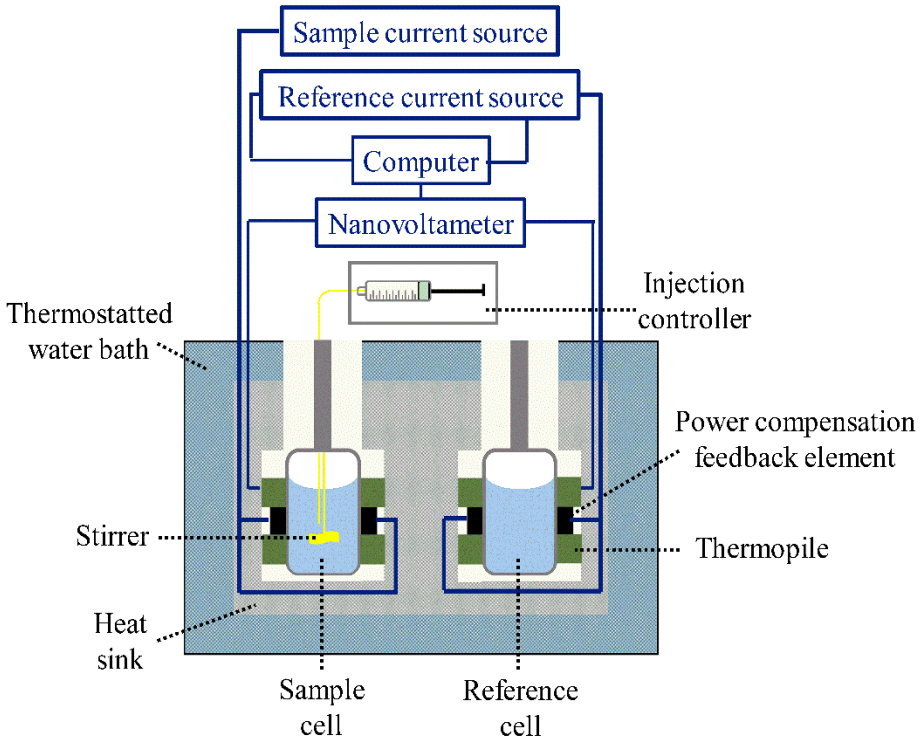
changes accordingly to the extent of the binding, using techniques such as fluorescence and UV-vis spectroscopy (RAWAT et al., 2019), and isothermal titration calorimetry (SCHMIDTCHEN, 2012), along with a mathematical binding model.

2.1.1 Isothermal titration calorimetry

The isothermal titration calorimetry (ITC) is one of the most useful techniques when it comes to studying binding processes since the physical observable measured by it is the heat involved in the interaction. That way, ΔH° can be obtained directly and in a single experiment, unlike the obtained through the van't Hoff plot[3].

To understand the fundamental principles of how the ITC operates we need to look at its main components, as shown in Fig. 1.4.

Fig. 1.4. Schematic of the principal components of an isothermal titration calorimeter.

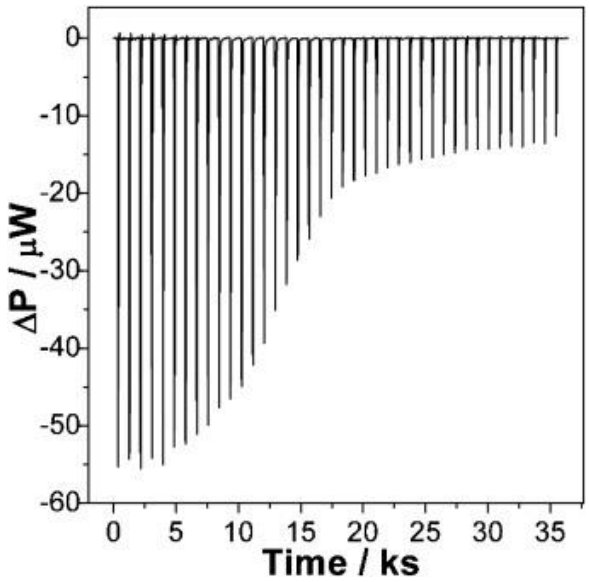


Source: Adapted from FREIRE; MAYORGA; STRAUME, 1990.

[3] Dependence of the **ln K** with the temperature variation, where the enthalpy change is obtained through the slope of the curve.

Initially, the sample and reference cells are filled with a solution of the host molecule and the solvent used, respectively, while the solution containing the guest is added to a syringe that will be used for the titration. Then, all the components inside the calorimeter are brought to thermal equilibrium in a chosen temperature, and the experiment is performed isothermally, with the assistant of the thermostatted bath. Beginning the experiment, when small aliquots (in the order of μL) of the guest solution is added to the sample cell (containing 2.7 mL of the host solution), the energy absorbed or released in the binding process causes a variation of the cell's temperature, which generates a temperature difference between the cell and the heat sink (a metal mass in thermal equilibrium with the thermostatted bath). This difference causes a heat flow, between the cell and the heat sink, that passes through the thermopile, located between these two components. The result is an electric potential that is proportional to the temperature difference which is also proportional to the heat flow. This electric potential is then measured by a nanovoltameter which sends the information to a computer. Since the thermopiles of the sample and reference cells are connected electrically opposed, the calorimeter measures the difference between the heat absorbed or released by the cells, eliminating environmental errors. Finally, with the assistant of the power compensation feedback element, the computer adjusts the current applied to the cells, in order to compensate for the temperature difference generated by the binding and dilution processes, returning the temperature difference between the two cells to the baseline. Thus, the rate of applied heat flow (also known as power, ΔP) in function of time (t), necessary to return the calorimeter to its steady-state temperature difference, after each injection, is used to produce the calorimetric raw data (Fig. 1.5).

Fig. 1.5. Calorimetric raw data obtained for an interaction experiment, where a 1-dodecylpyridinium chloride solution (66.4 mM) was titrated into a β-cyclodextrin solution (2.1 mM), at 298.15 K.



Source: AGUDELO et al., 2019.

The procedure described above is related to the interaction experiment, in which the data obtained will possess the contribution of the guest dilution in the sample cell. To discount this contribution, a second experiment is made, in which the guest solution is titrated into the sample cell containing only the solvent used, i. e., in the absence of the host molecule.

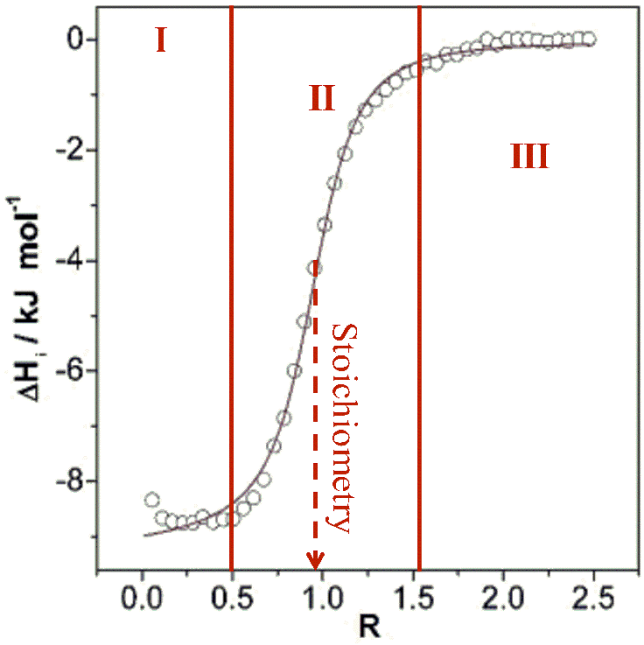
Then, the integration of peaks obtained in the calorimetric raw data results in the heat (q) involved in the processes occurring in the sample cell, after each injection, as shown below

$$q = \int \Delta P \, dt \tag{3}$$

In the interaction experiment, the heat (q_{int}) obtained has contributions from (i) the guest's dilution and (ii) the processes that lead to the complex formation (as described in section 2). Since the energy of (i) is obtained in the dilution experiment (q_{dil}), the heat associated only with the complex formation (q_i) is obtained by subtracting q_{dil} from q_{int}, for each injection.

Moreover, since the experiments are performed at constant pressure, q_i is equal to the system's enthalpy change, and dividing these values by the quantity of guest molecule (n_G) added to the sample cell, after each injection, we obtain the enthalpy change per mole of guest (ΔH_i). Through plotting the dependence of ΔH_i with the molar ratio ($R = n_G/n_H$, where n_H is the quantity of host molecules), we obtain a Wiseman isotherm (Fig. 1.6), which is useful for interpreting the obtained data.

Fig. 1.6. Wiseman isotherm for the formation of complexes between 1-dodecylpyridinium chloride and β-cyclodextrin, at 298.15 K.



Source: Adapted from AGUDELO et al., 2019.

As can be seen, the Wiseman isotherm possesses a sigmoidal shape, that can be analyzed through three regions. In region I, corresponding to the initial injections, the host molecule present in the sample cell is in excess, consequently, almost every guest molecule added is complexed. However, as the guest's concentration is increased in the cell, the number of free host molecules is reduced and the complexes reach the stoichiometry (region II). After the stoichiometry is reached, the number of free host molecules continues to decrease, while the number of free guest molecules increases until it reaches the excess in solution (region III), in which almost no new complex is formed with the further addition of guest.

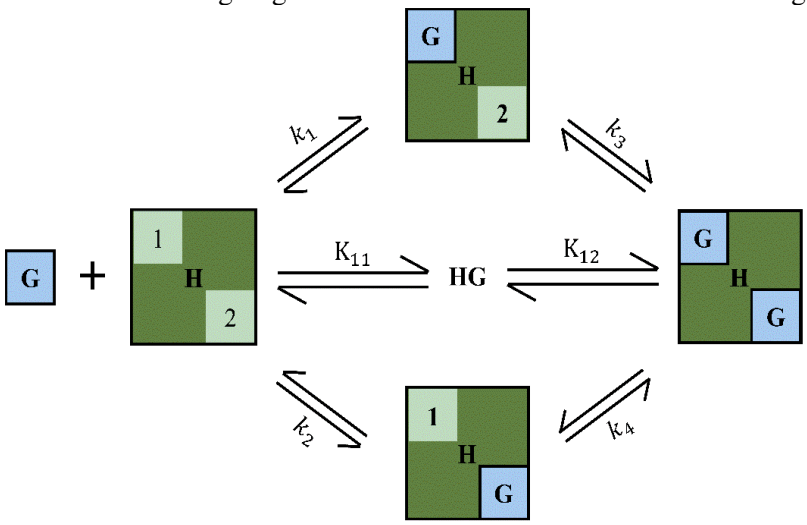
Besides that, through the Wiseman isotherm, the thermodynamic parameters (binding constant, stoichiometry and standard enthalpy change) of the complexes formed can be obtained. This, however, is only possible with the help of a mathematical binding model, which provides the parameters upon fitting the data.

2.1.2 Single set of identical sites model

The most used binding model for studying the formation of host-guest complexes, through ITC, is the single set of identical sites (SSIS). To derive this mathematical model, fist we need to comprehend some concepts.

Consider the binding of a guest to a host with n identical and independent sites, i. e., the affinity of the guest for all host's sites is identical and once the binding occurs, the other sites are not affected by it. As exemplified by Scheme 1.2, the binding of the guest to each binding site will be described by an equilibrium constant, named microscopic or intrinsic constant (k). However, as mentioned, the binding sites are identical and independent, so $k_1 = k_2 = k_3 = k_4 = \cdots = k_n = k_b$, in other words, the binding process can be described by one single microscopic constant k_b.

Scheme 1.2. The binding of guest molecules to a host with $\boldsymbol{n = 2}$ binding sites.



Source: Adapted from MARTINEZ et al., 2013.

Thus, a new variable, named binding parameter ($\bar{\nu}$), needed for deriving the model, can be described in terms of k_b. This parameter represents the moles of bound guest (n_G^b) by each mole of host (n_H^t), assuming values between 0 and **n,** and by a series of substitutions (shown in detail by MARTINEZ et al., 2013), $\bar{\nu}$ becomes dependent of k_b, the number of host's binding sites and the free guest concentration, as follows:

$$\bar{\nu} = \frac{n_G^b}{n_H^t} = \frac{[G]_b}{[H]_t} = \frac{nk_b[G]}{1 + k_b[G]} \qquad (4)$$

where $[G]_b$ is the bound guest concentration and $[H]_t$ is the total host concentration.

Now, the heat involved in each injection of a calorimetric experiment can be related to the standard enthalpy change in the following way

$$q_i = \Delta H° \Delta n_G^b \tag{4}$$

where Δn_G^b is the is the amount of guest bounded in the injection i, that is $\Delta n_G^b = n_{G,i}^b - n_{G,i-1}^b$. However, we can also express the moles of guests bound in terms of concentration, and consequently, in terms of the binding parameter, as shown below

$$q_i = \Delta H° \, V_c([G]_{b,i} - [G]_{b,i-1}) = \Delta H° \, V_c(\bar{\nu}_i[H]_{t,i} - \bar{\nu}_{i-1}[H]_{t,i-1}) \tag{5}$$

where V_c represents the sample cell's effective volume. Therefore, the total heat (Q_T) accumulated after N injections is given by

$$Q_T = \sum_{i=1}^{N} q_i = \Delta H° V_c [H]_t \bar{\nu} = \Delta H° V_c [H]_t \frac{n k_b [G]}{1 + k_b [G]} \tag{6}$$

As the $[G]$ is an unknown variable during the calorimetric experiment, it's necessary to estimate its value through experimental variables, such as the total guest concentration $[G]_t$ and Q_T as

$$[G] = [G]_t - [G]_b = [G]_t - \frac{Q_T}{\Delta H° V_c} \tag{7}$$

Finally, by substituting Eq. 7 in Eq. 6, a quadratic equation is obtained where Q_T is the unknown variable, whose solution is given by

$$Q_T = \frac{V_c \Delta H°}{2k_b} \left[1 + k_b [G]_T + n k_b [H]_T - \sqrt{(1 + k_b [G]_T + n k_b [H]_T)^2 - 4 n k_b{}^2 [H]_T [G]_T} \right] \tag{8}$$

and the heat associated with each injection is obtained through

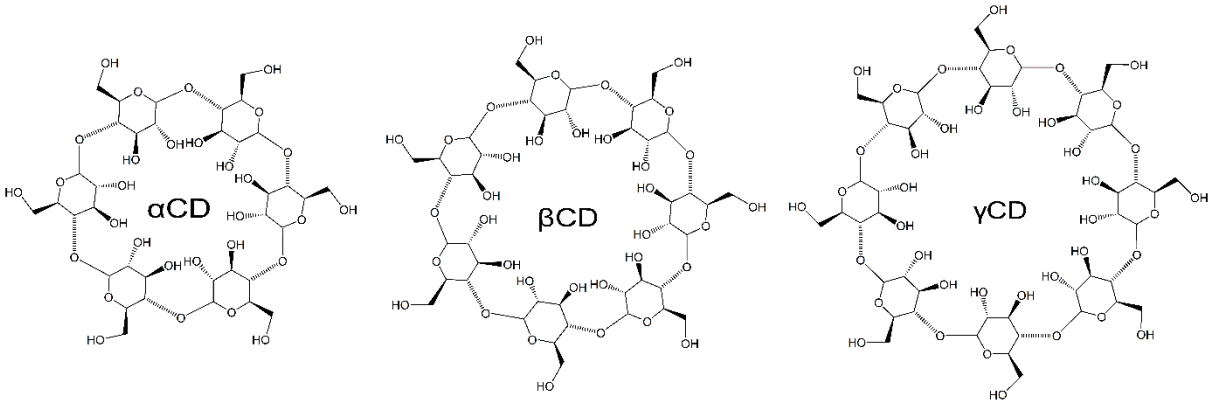
$$q_i = \Delta Q_T = Q_T(i) - Q_T(i-1) + \frac{V_{inj}}{V_c}\left(\frac{Q_T(i) + Q_T(i-1)}{2}\right) \quad (9)$$

where $Q_T(i)$ and $Q_T(i-1)$ are the total heat accumulated after the ith and $(i-1)$th injections and V_{inj} is the injection volume. Thus, with Eqs. 8 and 9, the experimental data obtained in the ITC experiment is fitted, using appropriate software, and the unknown variables of Eq. 8 (k_b, $\Delta H°$, and n) are determined. As for the other thermodynamic parameters ($\Delta G°$ and $\Delta S°$), they're calculated using Eqs. 1 and 2.

3 Cyclodextrin and inclusion complexes

A great variety of molecules can be used as a host in HG complexes, such as proteins, cryptands, crown ethers, cucurbiturils, pillararenes, and cyclodextrin (CDs), which are the most commonly used. CDs are cyclic oligosaccharides obtained through the enzymatic degradation of starch, being isolated for the first time by Villiers, in 1891. These macrocyclic molecules are formed by α(1-4)-linked glucopyranoside units, the most stable being the ones with 6 (αCD), 7 (βCD), and 8 (γCD) units, as shown in Fig. 1.7. However, among the native CDs, the most used in studies is βCD due to its easy purification and, consequently, lower cost, and the capacity to interact with a great number of molecules.

Fig. 1.7. Structure of αCD, βCD, and γCD.

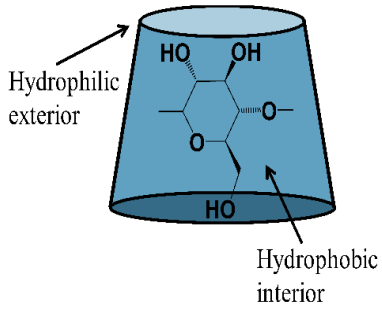


Source: The author.

Due to the chair conformation of the glucopyranose units, the CDs possess a truncated cone shape (Fig. 1.8), where the secondary hydroxyl groups are located on the wider edge, and

the primary ones on the narrow edge (MURA, 2014). Then, depending on the number of glucopyranose units, the CDs will have different sizes, as well as other properties, as shown in Table 1.2.

Fig. 1.8. The truncated cone shape of cyclodextrins.



Source: The author.

Table 1.2. Cyclodextrins properties.

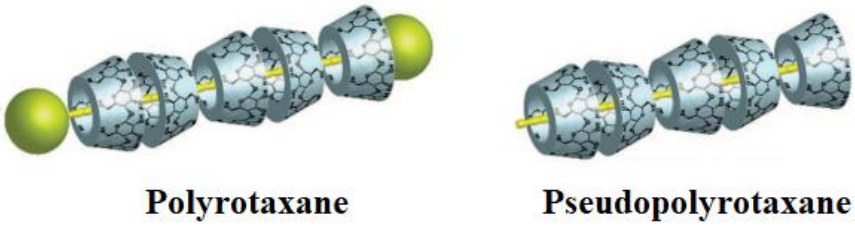
Property	**αCD**	**βCD**	**γCD**
Number of glucopyranose units	6	7	8
Molecular weight (g mol^{-1})	972	1135	1297
Solubility in water at 298.15 K (% w/w)	14.5	1.85	23.2
Outer diameter (Å)	16.6	15.4	17.5
Cavity diameter (Å)	4.7-5.3	6.0-6.5	7.5-8.3
Height of torus (Å)	7.9	7.9	7.9
Cavity volume ($Å^3$)	174	262	427

Source: Adapted from DEL VALLE, 2004.

Since the CDs' cavity is composed of the hydrogen atoms and the glycosidic oxygen bridges, it assumes a lipophilic character. Thus, the hydrophilic exterior and hydrophobic interior are responsible for the water solubility and ability to accommodate hydrophobic molecules, respectively, forming HG complexes, which in this case are also known as inclusion compounds, since the guest molecule is encapsulated by a cavity-containing host. Consequently, with the formation of inclusion complexes, chemical and physical properties of the guests are changed, such as stabilization of light- or oxygen-sensitive substances (IOELE et al., 2017), modification of the chemical reactivity (NUÑEZ-LOPEZ et al., 2019), improvement of solubility (AYTAC; UYAR, 2017), protection against degradation by microorganisms (PILETTI et al., 2019), masking of smell, taste, pigments or color (FENYVESI; SZENTE, 2016), etc.

Besides the formation of simple inclusion complexes, CDs can also be used for constructing molecules with different architectures, such as rotaxanes, polyrotaxanes or pseudopolyrotaxanes (Fig. 1.9). These structures consist of an axis threaded by of one or more macrocyclic molecules, in which the dissociation of the molecules can be hindered by a bulky group (called stoppers), in the case of rotaxanes and polyrotaxanes, or not, in the case of pseudopolyrotaxanes (WENZ; HAN; MÜLLER, 2006).

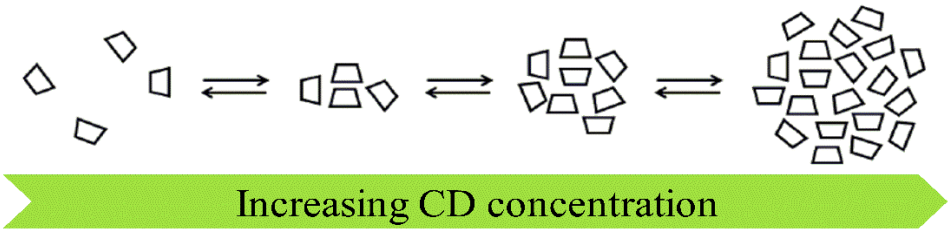
Fig. 1.9. Schematic illustration of CD-based polyrotaxane and pseudopolyrotaxane.



Source: Adapted from HARADA et al., 2009.

Finally, despite the hydrophilic exterior, CDs also have been found to self-assemble in solution, which was first observed for α and γCD (MIYAJIMA; SAWADA; NAKAGAKI, 1983), however later works have showed βCD also aggregates (COLEMAN et al., 1992). The size of these structures increases by increasing the CD's concentration, varying generally from 20 to 200 nm, which is represented in Fig. 1.10.

Fig. 1.10. Representation of the self-association of CDs into structures with varying sizes.



Source: Adapted from LOFTSSON; SAOKHAM; SA COUTO, 2019.

In the case of βCD, some studies diverge on the value of the critical aggregation concentration (CAC), however for all of them βCD forms aggregates in concentrations well below its maximum solubility (~16 mM), and with varying sizes, depending on the concentration as shown in Table 1.3.

Table 1.3. CAC and size of βCD aggregates, at 298.15 K.

CAC / mM	Size / nm	Reference
1.6	60-120	(DE SOUSA et al., 2012)
3	90	(BONINI et al., 2006)
~5.6	-	(SAOKHAM et al., 2016)

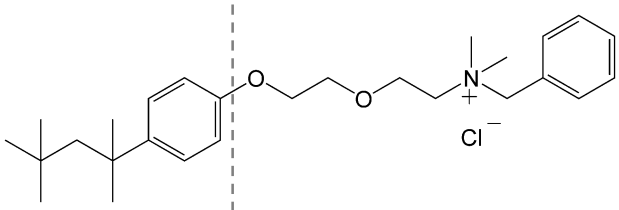
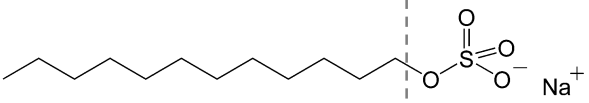
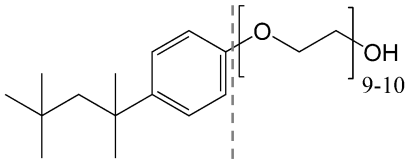
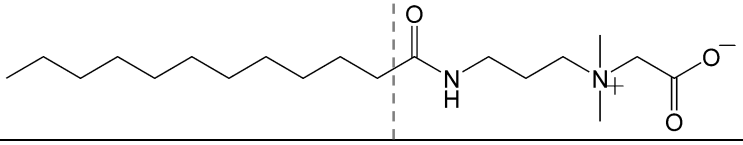
Moreover, the presence of a guest molecule may induce the CDs aggregation (COUTO et al., 2019; MESSNER et al., 2011; STAPPAERTS et al., 2017), or even the inclusion complexes formed may as well self-assemble (LOFTSSON; SAOKHAM; SA COUTO, 2019; RYZHAKOV et al., 2016). However, both these aggregates may be transient in solution and dissociate upon dilution, making difficult the detection.

4 Surfactants

Among the several molecules or ions, such as drugs (ZHANG et al., 2019), dyes (SEMERARO et al., 2015), flavonoids (DOS SANTOS LIMA et al., 2019), polymers (MARTINEZ-TOME et al., 2013), alkylammonium ions (LIPPMANN et al., 1993), and alkali-metal cations (HOFFMANN et al., 1994), that can be used as guest in HG complexes, the surfactants are a class of compounds that have been a constant research target over the years due to the fundamental information provided by the complexes based on these molecules (as will be seen in section 5). These amphiphilic molecules, also known as surface-active agents, are formed by a hydrophobic tail and a hydrophilic head group, which determines if the surfactant is ionic (cationic or anionic), nonionic or zwitterionic[4] (Table 1.4).

[4] A zwitterion is a neutral chemical species that possess opposite charges in different atoms.

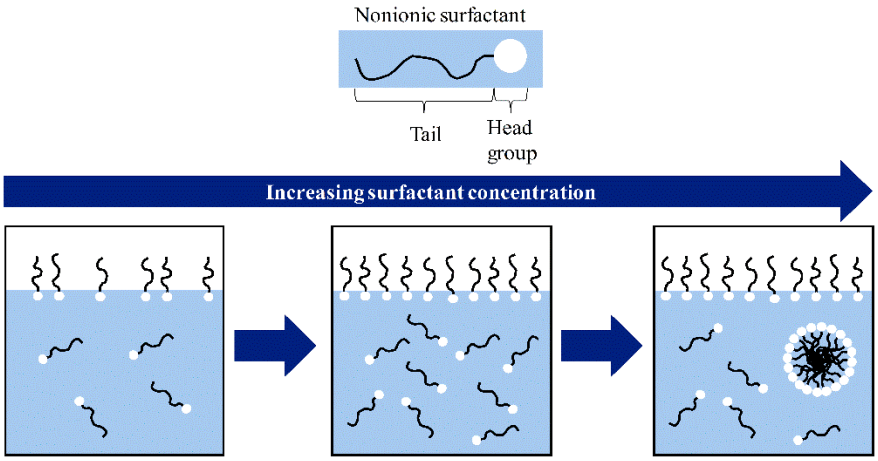
Table 1.4. Structure and type of the surfactants: (a) benzethonium chloride, (b) sodium dodecyl sulfate, (c) Triton X-100, and (d) lauramidopropyl betaine.

	Tail	Head group	Type
(a)			Cationic
(b)			Anionic
(c)			Nonionic
(d)			Zwitterionic

In aqueous solutions, until a certain concentration, the surfactants are located preferably in the system's interface, where the head group is oriented to the solution, while the tail is oriented to the other phase (for instance the air), which cause the system' surface tension[5] to decrease. However, with the increase of the surfactants' concentration, the decrease of the surface tension will occur until the interface is energetically saturated. When this occurs, the surfactant reaches the critical micelle concentration (CMC), in which any more surfactant added will not go to the interface, but self-assemble in solution forming micelles (Fig. 1.11).

[5] An excess of Gibbs free energy per area, originated from the unfavorable interactions and different configurations of the molecules present in the system's interface, in comparison to the phases.

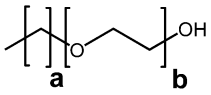
Fig. 1.11. Micellization of a nonionic surfactant.



Source: The author.

Due to the micelles' structure (a hydrophobic core formed by the surfactants' tail, and a surface formed by the head groups and, in the case of ionic surfactants, by some counterions), this compounds can encapsulate hydrophobic molecules and, thus, be used in separations (HASSANIEN et al., 2016), catalysis (GHOSH; SETH; PURKAYASTHA, 2019), and drug delivery systems (LU et al., 2018). Micelles based on nonionic surfactants are particularly useful in applications, especially as drug carriers, due to their non-toxicity, low cost, and biocompatibility (ULLAH et al., 2014), which is the case of the Brij surfactants (ZATZ, 1989). Brij is the commercial name of the nonionic surfactants that consist of a head with varying units of ethylene oxide, and a tail consisting of a polymethylene chain (SOWMIYA; TIWARI; SAHA, 2010), as shown in Scheme 1.3 where the surfactants used in this dissertation are presented.

Scheme 1.3. Structure of the Brij surfactants, where **a+1** is the number of carbon atoms in the alkyl chain, and **b** is the number of ethylene oxide units.



Brij 56	Brij 58	Brij 76	Brij 78
a=15, **b**=10	**a**=15, **b**=20	**a**=17, **b**=10	**a**=17, **b**=20

As the majority of nonionic surfactants, the Brij family also possess low values of CMC, in comparison with the values for ionic surfactants, which is an advantage when using these molecules as carries, since the amount of material necessary for the application will be low. For

instance, the CMC of sodium dodecyl sulfate is ~8 mM [ref], while for the surfactants used here (Brij 56, Brij 58, Brij 76, and Brij 78) the CMC values range from 0.089 to 0.029 mM (WALTERS; DUGARD; FLORENCE, 1981).

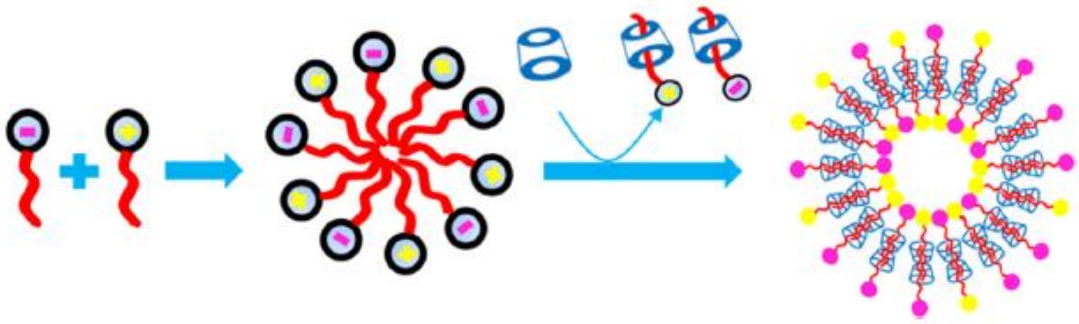
5 Interaction cyclodextrin-surfactant

The study of HG complexes formed by the interaction between CDs and surfactants show many advantages in both the fundamental and application point of view. In the first case, this interaction allows the evaluation of how the hydrophobic/hydrophilic balance contributes to the formation of HG complexes since the surfactant's tail and head group can be varied. For instance, studies show the more hydrophobic the surfactant's tail, the greater is the complexes' stability, which is shown in the work of Wilson and Verral, where the binding constant for the interaction between βCD and five $C_xH_{2x-1}CO_2Na$ surfactants ranged from 6.0 x 10^1 M^{-1} (when x=6) to 6.3 x 10^4 M^{-1} (when x=14) (WILSON; VERRALL, 1998). In contrast, Benkő and Király (2012) studied the inclusion complexes formed between βCD and surfactants with different head groups (cationic, anionic and nonionic), but the same alkyl chain length, finding the stability of all complexes to be similar ($\Delta G° \approx$ -24 kJ mol^{-1}). Moreover, for all surfactants used, the interaction processes, at 298 K, were enthalpically and entropically favorable.

As for the application point of view, it is well known that the presence of CD increases the CMC value of some surfactants since the encapsulation of the hydrophobic tail prevents the aggregation (JIANG et al., 2003). Thus, knowing how this interaction affects the properties of each molecule is of great importance when using them together.

With the continuous research on this topic, over the years, new features of this type of HG complex have been reported. For instance, recent works have showed the addition of βCD in a mixed ionic surfactant system induces a micelle-to-vesicle transition (DAI et al., 2016; JIANG et al., 2009; YANG et al., 2019) (Fig. 1.12), showing the previous concept of micelle rupture by the formation of inclusion complexes is not true for all systems. Moreover, another constructive effect resulting from this interaction was the increase of the viscoelasticity and gelation behavior of some nonionic surfactants when in the presence of native and/or substituted CDs (DA SILVA et al., 2013; GARCÍA-PÉREZ et al., 2014; PRADAL et al., 2013).

Fig. 1.12. Schematic aggregate transition in mixed cationic/anionic surfactant systems induced by βCD.



Source: DAI et al., 2016.

The interesting findings shown above are still recent, thus the study of the formation of inclusion complexes in the micellar region is still lacking (TSIANOU; FAJALIA, 2014), especially the thermodynamic aspect, since the majority of studies focus on the pre-micellar concentration of the surfactants (VALENTE; SÖDERMAN, 2014). However, from the few works reported, very interesting information has been discovered. For instance, Ghosh, Seth and Purkayastha (2019) found that CD-surfactant inclusion complexes form "hydrated micelles" that allow the further penetration of water molecules in the micelle's core.

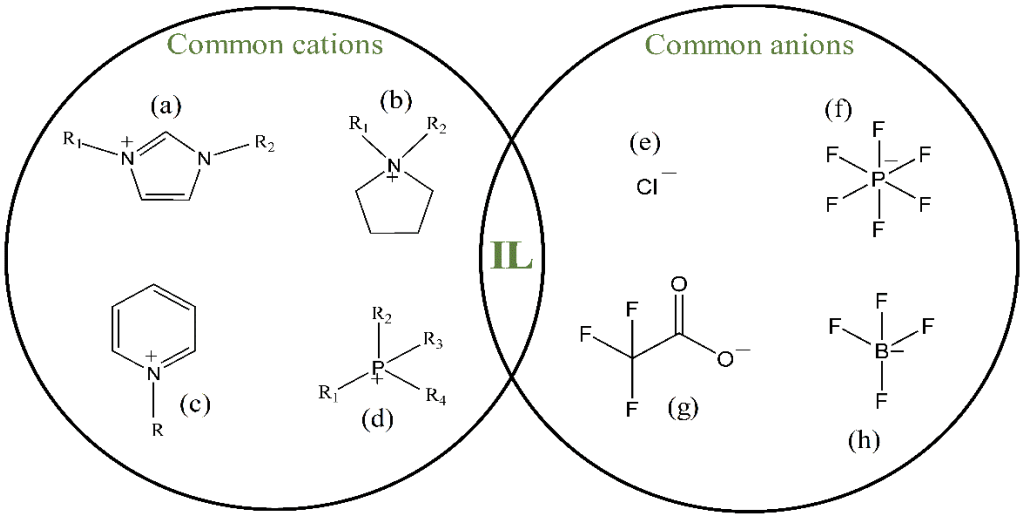
Moreover, since the desolvation of the molecules plays an important role in the formation of hos-guest complexes, studying the presence of cosolvents or cosolutes in the system is also essential, since they can change the organization of the solvent molecules. However, there are few works in the scientific literature where this study is made, especially involving nonionic surfactants. For instance, studies involving the effect of organic cosolvents such as butanol (RAFATI; SAFATIAN, 2008), ethanol, N-methylacetamide (OKUBO; KITANO; ISE, 1976), and isopropanol (MARTIN et al., 1995), as well as, cosolutes such as sodium chloride (CZAPKIEWICZ; TUTAJ, 1993), and 1-alkyl-3-methylimidazolium chloride (AGUDELO et al., 2019) have been reported, but only for the interaction between CD and ionic surfactants.

6 Ionic liquids

In the last 20 years, the ionic liquids (ILs) have been drawing attention due to their great application potential. These compounds are organic or semi-organic salts, however, differently from other salts, they melt at temperatures lower than 398.15 K. Due to their low volatility, non-flammability, tunable viscosity, electrolytic conductivity and stability in air and water, they were initially denominated as green solvents, but it is known today that not all ILs possess these

features, which are dependent of the salt composition. Thus, the combination of different cations and anions (Fig. 1.13) allows the design of IL with properties suitable for a variety of applications such as separations (HAN; ARMSTRONG, 2007), as battery electrolytes (LEWANDOWSKI; ŚWIDERSKA-MOCEK, 2009), in the production of nanomaterials (LI et al., 2008), in catalysis (WELTON, 2004), as industrial solvents (ROGERS; SEDDON, 2003), and in controlled drug delivery (SHAMSHINA; BARBER; ROGERS, 2013).

Fig. 1.13. Common cations ((a) imidazolium, (b) pyrrolidinium, (c) pyridinium, and (d) tetraalkylphosphonium) and anions ((e) chloride, (f) hexafluorophosphate, (g) trifluroacetate, and (h) tetrafluoroborate) that compose ionic liquids.



Source: Adapted from SUN; ARMSTRONG, 2010.

Although promising the use of these compounds, it is important to know how they affect the system they are in, especially when they are being used for pharmaceutical purposes. Thus, some papers have investigated the effect of ILs in a variety of processes, such as protein denaturation (BAKER; HELLER, 2009), interaction protein-ligand (AZEVEDO et al., 2013), micellization (AGUDELO et al., 2020), and formation of host-guest complexes (TRAN; DE PAOLI LACERDA, 2002). However, currently, only the work of Agudelo et al. (2019), has reported how the presence of ionic liquids affects the CD-surfactant interaction, in which they found the presence of imidazolium ILs destabilizes the complex formed between βCD and 1-dodecylpyridinium.

7 Reference

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CHAPTER 2: Formation and self-association of host-guest complexes based on βCD and nonionic surfactants Brij

1 Introduction

Host-guest compounds have been a constant topic of study in supramolecular chemistry, due to the variety of molecules that can be used as interacting partners to form a myriad of new structures (HUANG; ANSLYN, 2015). Among the different type of structures formed, a really interesting class are the inclusion compounds, since the complexation occurs via the encapsulation of the guest molecule by a cavity-containing host. Through this interaction, organic guests may have their properties modified, such as solubility, stability and volatility, which makes these complexes so interesting for applications in pharmaceutical, food, textile, and cosmetic industries.

Amidst the diversity of macrocyclic molecules that behave as hosts, cyclodextrins (CDs) are the most commonly used due to its ability to form complex with drugs (ZHANG et al., 2019), flavonoids (DOS SANTOS LIMA et al., 2019), dyes (SEMERARO et al., 2015), food ingredients (SZENTE; SZEJTLI, 2004), polymers (MARTINEZ-TOME et al., 2013), surfactants (VALENTE; SÖDERMAN, 2014), etc. CDs are cyclic oligosaccharides, obtained through the enzymatic degradation of starch, consisting of α(1-4) linked D-(+)-glucopyranose units, which assume a truncated cone shape. The most stable CDs are the ones with 6 (αCD), 7 (βCD), and 8 (γCD) glucopyranoside units, being βCD the most used due to its low cost and capacity of interacting with a greater number of molecules (CRINI et al., 2018). Owing to the arrangement of the functional groups in the CD ring (the C-H bonds pointing inward and the hydroxyl groups located at the rim), the cavity and exterior assume a hydrophobic and hydrophilic feature, respectively. In that way, the lipophilic cavity provides a microenvironment that can accommodate the hydrophobic moieties of a guest molecule. However, despite the hydrophilic exterior, native and modified CDs self-associates in solution, forming structures with 10-200 nm depending on the CD's type and concentration (BONINI et al., 2006; COUTO et al., 2019; DO; VAN HOOGHTEN; VAN DEN MOOTER, 2017; GONZÁLEZ-GAITANO et al., 2002). Besides that, it can be found in the scientific literature various works reporting the aggregation of CD-based inclusion complexes, leading to the formation of different types of structures, such as rods, spheres, bilayers, vesicles and reversible micelles (DE SOUSA et al., 2008; LOFTSSON; SAOKHAM; SA COUTO, 2019; RYZHAKOV et al., 2016).

In view of the diversity of properties shown by CD-containing systems, herein, we report the interaction between βCD and different nonionic surfactants. The study of inclusion complexes where surfactants are used as guest molecules is of great importance since the amphiphilic feature of this molecules allows the investigation of how the hydrophobic/hydrophilic balance influences the interaction process. Moreover, recent studies have shown the interaction between CDs and surfactants results in a micelle-to-vesicle transition [ref], and increase of the viscoelasticity and gelation behavior of nonionic surfactants. Thus, four Brij surfactants (commercial name for polyethoxylated fatty alcohols) with varying head group (polyethylene oxide (PEO)) and tail (aliphatic chain) lengths were used here. Besides the new information the interaction Brij-βCD could provide about the formation of host-guest complexes, only a few studies in the literature have reported such interaction (POPOVA; TOPCHIEVA, 2001; TOPCHIEVA; KAREZIN, 1999a, 1999b), especially using a thermodynamic approach (BUSCHMANN; JANSEN; SCHOLLMEYER, 2000; HE et al., 2008). Moreover, the effect of the ionic liquid (IL) 1-butyl-3-methylimidazolium chloride (C_4mimCl) on the inclusion process was study in order to obtain valuable information on how supramolecular systems form, especially in aqueous medium, since the presence of cosolutes can affect the 3D water structure and, consequently, alter the interaction between the molecules present in the solution.

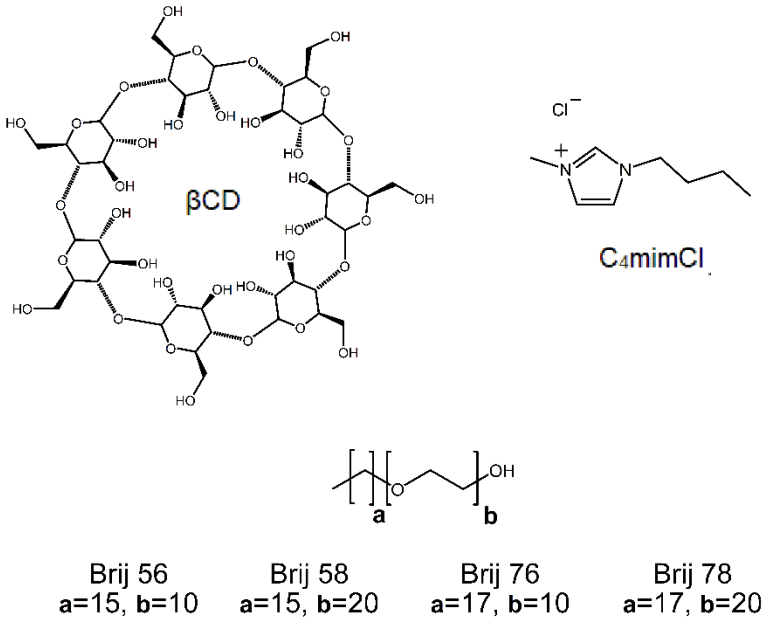
For this, the isothermal titration calorimetry and dynamic light scattering techniques were used to provide the thermodynamic and structural information imperative to comprehend the molecular recognition process involved in the inclusion process.

2 Materials and methods

2.1 Materials

β-cyclodextrin (βCD) (>97%), 1-butyl-3-methylimidazolium chloride (C_4mimCl) (>98%), poly(ethylene oxide)-(10)-cetyl-ether (Brij 56), poly(ethylene oxide)-(20)-cetyl-ether (Brij 58), poly(ethylene oxide)-(10)-stearyl-ether (Brij 76), and poly(ethylene oxide)-(20)-stearyl-ether (Brij 78) were purchased from Sigma Aldrich (St. Louis, MO, USA). The structure of the chemical species are shown in Scheme 2.1. All materials were used without further purification. The solutions were prepared using deionized water obtained in a Milli-Q system from Millipore (Burlington, MA, USA).

Scheme 2.1. Chemical structures of βCD, C_4mimCl, and the Brij surfactants, where **a** and **b** represent the number of carbon atoms and EO units, respectively.



2.2 Methods

2.2.1 Isothermal Titration Calorimetry

The calorimetry measurements were performed in a thermal activity monitor (TAM III, model) from TA Instruments (New Castle, DE, USA), with two stainless steel cells for sample and reference, being the latter filled with deionized water. The experiments were performed at constant temperature (298.150000 ± 0.00001) and consisted of 50 injections, of 10 μL each, of a surfactant stock solution in 2.7 mL of a βCD solution 2.2 mM (interaction experiment) or deionized water (dilution experiment). The concentration of the Brij stock solutions were 2.81 mM (Brij 56), 3.38 mM (Brij 58), 2.01 mM (Brij 76), and 1.19 mM (Brij 78), and the experiments were carried out in the micellar region of the surfactants. The injections were made using a Hamilton syringe with a gold cannula controlled by a syringe pump provided by TA Instruments. The interval between injections was 15 min and the sample cell content was stirred at 180 rpm by a gold helix. For the effect of C_4mimCl on the interaction process, the stock solutions of surfactant and βCD were prepared using C_4mimCl solutions with different concentrations (10-1000 mM) as the solvent, and the experiments were performed as described

above. At the end of each experiment the calorimetric raw data (heat flow vs. time) was obtained.

2.2.2 Dynamic Light Scattering

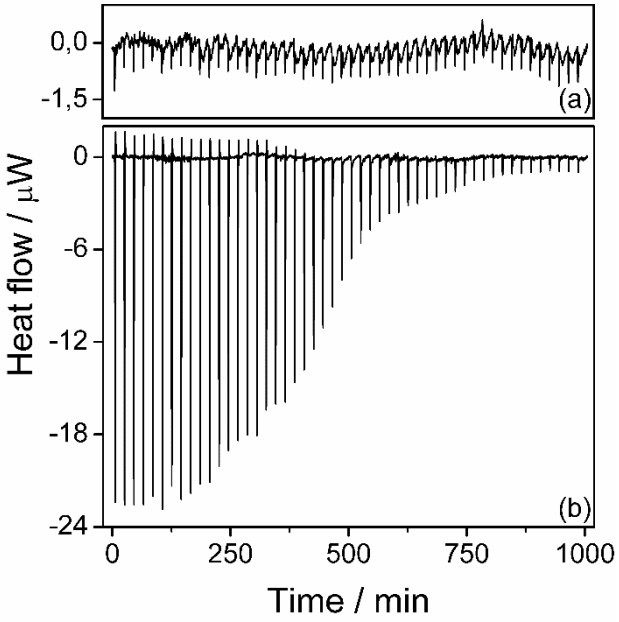
The size measurements were performed at 298.15 K using a Zetasizer Nano ZS system from Malvern Instruments Ltd (Worcestershire, UK), using disposable folded capillary cells. The instrument was equipped with a He/Ne laser with wavelength of 663 nm, and the scattered intensity was monitored under a detection angle of 90°. For the experiments, samples containing βCD, Brij micelles, or both were prepared using deionized water previously filtered through a 0.45 μm Millipore filter.

3 Results and Discussion

3.1 Interaction between βCD and the Brij surfactants

The thermodynamic characterization of the interaction between βCD and the Brij surfactants was performed by ITC, which is an accurate technique for studying the formation of host-guest complexes, since it allows the direct measurement of the heat (q) involved in the process, in addition to the determination of the thermodynamic parameters in a single titration curve (ONNAINTY et al., 2013; VALENTE; SÖDERMAN, 2014). Fig. 2.1 shows the thermograms obtained from the dilution of Brij 56 in water (Fig. 2.1a) and interaction with βCD (Fig. 2.1b). Similar thermograms were obtained for the interaction and dilution of the other surfactants (Fig. A1-A3).

Fig. 2.1. Calorimetric raw data obtained from the titration of a Brij 56 solution (2.81 mM) in (a) deionized water and in (b) a βCD solution (2.20 mM), at 298.15 K.



The integration of the peaks obtained in the thermograms gives the values of q for each injection of surfactant. Although the calorimetric experiment was carried out in the micellar region of all Brij surfactants, the energy involved in the disassembly of Brij micelles into monomers was negligible, as it can be seen in the dilution experiment thermograms (Fig. 2.1a and Fig. A1-A3), where no micellization profile was observed. Thus, at each injection, the heat associated only with the binding process (q_i) was calculated by simply discounting the surfactant's dilution heat from the values obtained in the Brij 56-βCD interaction experiment ($q_i = q_{int} - q_{dil}$). The total heat accumulated (Q_T) in the binding process, after N injections, is given by Eq. 1.

$$Q_T = \sum_{i=1}^{N} q_i \tag{1}$$

Assuming that the binding of the βCD to the surfactant occurs in m identical and independent binding sites (Brij + mβCD $\rightleftharpoons$ Brij-βCD$_m$), Q_T can be described as a function of the total surfactant concentration, according to the single set of identical sites (SSIS) model (MARTINEZ et al., 2013), as shown in Eq. 2.

$$Q_T = \frac{V_c \Delta H^\circ}{2k_b}\left[1 + k_b[\mathrm{Brij}]_T + nk_b[\beta\mathrm{CD}]_T - \sqrt{(1 + k_b[\mathrm{Brij}]_T + nk_b[\beta\mathrm{CD}]_T)^2 - 4nk_b{}^2[\beta\mathrm{CD}]_T[\mathrm{Brij}]_T}\right] \quad (2)$$

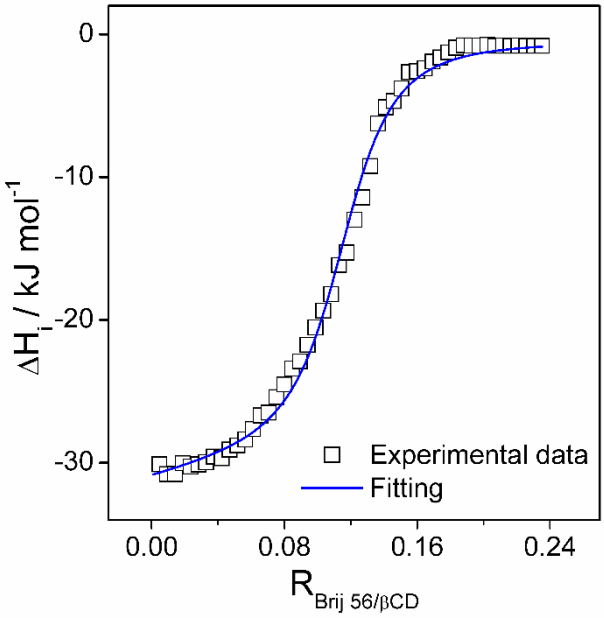
where V_c is the cell volume, $[\mathrm{Brij}]_T$ and $[\beta\mathrm{CD}]_T$ are the total concentration of surfactant and βCD in the cell after N injections, respectively. k_b and ΔH° are the intrinsic binding constant, and intrinsic standard enthalpy change, respectively, while n is the fraction of surfactant interacting with βCD, being $n = 1/m$. In the SSIS model, the binding strength of each βCD present in the complex is considered to be the same, in this way, the intrinsic thermodynamic parameters have the same values for all 1:j stoichiometries ($j = 1,2, \ldots, m$) (BROCOS et al., 2011).

Finally, the heat associated with each injection can also be expressed by Eq. 3,

$$q_i = \Delta Q_T = Q_T(i) - Q_T(i-1) + \frac{V_{inj}}{V_c}\left(\frac{Q_T(i) + Q_T(i-1)}{2}\right) \quad (3)$$

where $Q_T(i)$ and $Q_T(i-1)$ are the total heat accumulated after the ith and $(i-1)$th injections and V_{inj} is the injection volume. Therefore, through Eqs. 2 and 3, the thermodynamic parameters were determined by the application of the non-linear least square method on the data obtained, where k_b, ΔH°, and n were the unknown variables. Fig. 2.2 shows the experimental data (Wiseman isotherm) and the best fitting obtained from the SSIS model, for the interaction between Brij 56 and βCD. For the other surfactants, the Wiseman isotherms are shown in Figs. A1c, B2c and B3c.

Fig. 2.2. Plot of ΔH_i versus the molar ratio ($R_{(Brij\ 56/\beta CD)}$) for the interaction of Brij 56 with βCD, at 298.15 K, and the best fitting obtained from the SSIS model.



From the values of k_b and ΔH°, the intrinsic standard free energy change (ΔG°) and intrinsic standard entropy change (ΔS°) were calculated with Eqs. 4 and 5. All thermodynamic parameters related to the formation of complexes between βCD and Brij 56, as well as the other surfactants, are presented in Table 2.1.

$$\Delta G° = -RT \ln k_b \quad (4)$$

$$T\Delta S° = \Delta H° - \Delta G° \quad (5)$$

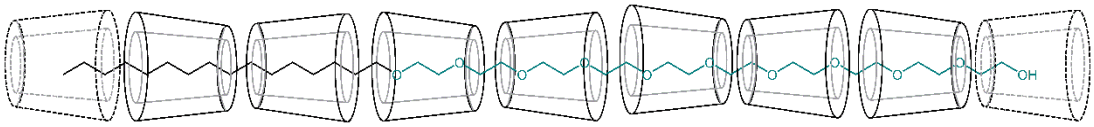
Table 2.1. Thermodynamic parameters obtained by ITC for the formation of host-guest complexes between βCD and Brij surfactants, at 298.15 K.

Brij	m	k_b	ΔG°	ΔH°	TΔS°
		10^5 L mol^{-1}	kJ mol^{-1}		
56	8.58 ± 0.07	2.08 ± 0.22	-30.35 ± 0.26	-31.18 ± 0.33	-0.83 ± 0.42
58	7.41 ± 0.05	3.08 ± 0.23	-31.33 ± 0.18	-42.25 ± 0.26	-10.92 ± 0.32
76	20.38 ± 0.28	0.77 ± 0.10	-27.89 ± 0.32	-31.4 ± 1.0	-3.5 ± 1.0
78	21.05 ± 0.18	13.6 ± 2.4	-35.0 ± 0.4	-46.7 ± 0.6	-11.7 ± 0.7

For the Brij 56-βCD complex, the results showed that 8 to 9 βCD are interacting with the surfactant. According to the standard stoichiometry of CD-based molecular necklaces, six atoms from the main chain of the guest molecule can be accommodated in one CD (HARADA, 1996). Thus, for Brij 56, which contains a tail of 16 carbons and a head group of 10 EO units,

7 βCD can be entirely threaded in the surfactant, while the last 2 βCD can encapsulate the remaining carbon atoms (Fig. 2.3). This result suggests that the inclusion process occurs in both hydrophobic and hydrophilic moieties of the surfactant.

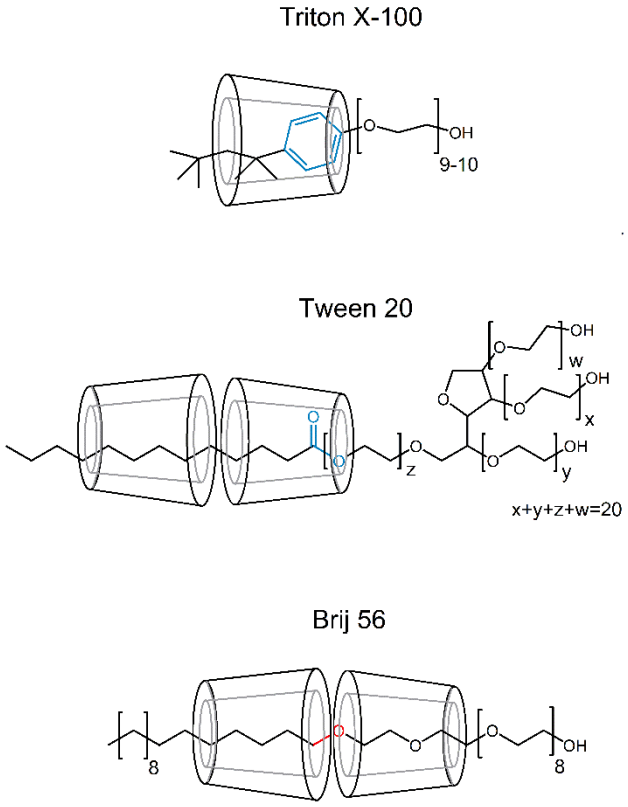
Fig. 2.3. Proposed structure of the βCD-Brij 56 complex. The aliphatic and EO chains are represented in black and dark cyan, respectively.



Although the majority of works, in the scientific literature, report that only αCD and γCD form inclusion complexes with PEO, due to the complementarity between the CD internal cavity and EO chain cross-sectional diameters (WENZ; HAN; MÜLLER, 2006), some studies have shown that βCD also includes this polymer. Buschmann, Jansen and Schollmeyer (2000) determined the thermodynamic parameters for the formation of complexes between βCD and PEO with different molecular weights, while Udachin, Wilson and Ripmeester (2000) characterized the structure of solid rotaxanes formed by these molecules. Moreover, studies on the interaction of βCD, or its modified forms, with PEO-containing nonionic surfactants have been reported. Popova and Topthieva (2001) observed, through X-ray diffraction, the formation of a crystalline complex between βCD and Brij 35 ($C_{12}H_{25}(OCH_2CH_2)_{23}OH$), finding later, through polarimetry measurements, a stoichiometry of ~1:8 (Brij 35:βCD), indicating that the hydrophobic and hydrophilic regions were encapsulated. Besides that, Alami et al. (2002). studied the formation of complexes between hydroxypropyl-βCD (HPβCD) with a nonionic heterogemini surfactant (NIHG750), which contains of two hydrophobic groups (two aliphatic chains with 9 carbon atoms and a cyano group in one of them) and two hydrophilic groups (a secondary hydroxyl group and a methyl-capped PEO chain with 16 EO units). The results obtained by small-angle neutron scattering indicated that HPβCD was also threaded in both regions of the surfactant. However, not all PEO-based nonionic surfactants, that form complexes with βCD, have their hydrophilic moiety included, which is the case of Triton X and Tween 20. Studies involving the formation of complexes between these two surfactants and βCD showed the host molecule interacts only with the hydrophobic moieties (MÜLLER; RITTER, 2012; ZHOU et al., 2013). Comparing the structure of these surfactants with the Brij series, it can be seen that both Triton X-100 and Tween 20 possess complementary groups to the βCD cavity, a benzene ring, and an ester, respectively (Fig. 2.4). The presence of these

groups may be preventing the migration of βCD molecules, from the tail to the head, due to a more intense interaction of these groups with the cavity, since van der Waals forces are distant-dependent interactions. Thus, the absence of a complementary group in the structure of Brij surfactants allows the encapsulation of the EO chain.

Fig. 2.4. Representation of the complexes of Triton X-100, Tween 20 and Brij 56 with βCD. The complementary groups of Triton X-100 and Tween 20 are shown in blue, while for Brij 56, the absence of such groups is represented in red.



To the extent of our knowledge, there is no study on the formation thermodynamics of Brij-βCD host-guest complexes. Therefore, to get more insight into how these complexes are formed, the thermodynamic parameters related to the interaction Brij 56-βCD will be discussed first. The k_b obtained for this complex was 2.08 x 10^5 M^{-1}, which is in agreement with the obtained by Buschmann, Jansen and Schollmeyer (2000) (10^5 M^{-1}), also using ITC. In contrast, He et al. (2008) could not evaluate the formation of a complex between the same molecules by fluorescence spectroscopy, using 2-(p-aminophenyl)-3,3-dimethyl-5-carboethoxy-3H-indole as a probe, suggesting that the interaction is weak. This shows how sensitive the ITC technique is for studying the formation of host-guest complexes.

From the k_b value determined here, negative ΔG° was obtained for the inclusion of the Brij 56 in βCD. This negative value indicates the predominance of the Brij 56-βCD complex over the free molecules in the thermodynamic equilibrium and results from the contribution of different processes occurring in the system, which the more relevant ones are the desolvation of Brij 56 molecule (**I**), and βCD cavity (**II**), the intermolecular interaction between them (**III**), and the conformational changes on the surfactant structure due to this interaction (**IV**). Although Brij 56 micelles might be breaking so the complexes may form, the energy involved in this process is negligible as shown previously, hence this process was not taken into account. In order to determine the driving force involved in the formation of the Brij 56-βCD complex, it is necessary to analyze their enthalpic and entropic contributions. The formation of the complex occurred with a decrease in the system's enthalpy and entropy. Despite the negative TΔS° value, the enthalpy decrease was greater, showing that the formation of the complex is enthalpy driven. ΔH° and TΔS° values can also be analyzed taking into account the contribution of the three processes described above. The process **I** occurs with an increase in enthalpy and entropy since highly structured water molecules are being released from the surfactant solvation shell to the bulk. The processes **II**, **III**, and **IV** occur with a decrease in enthalpy and entropy, due to the release of water molecules from the βCD cavity to the bulk, where the hydrogen bonding is more effective, interaction of the molecules via van der Waals forces, and the encapsulation of the EO chain, favoring the trans conformation over gauche (AHLNAES; KARLSTROEM; LINDMAN, 1987), respectively. Therefore, the ΔH° and TΔS° obtained indicate that **II**, **III** and **IV** are the main processes responsible for the formation of the Brij 56-βCD complex.

A similar analysis was made for the formation of complexes with the other surfactants. As can be seen in Table 2.1, the signal tendency of the thermodynamic parameters was maintained, however, their magnitude and the complexes' stoichiometries were affected by the differences in the Brij structure. Thus, a comparative analysis of the length of the hydrophobic moiety and the PEO fragment was carried out to better understand how these complexes are formed.

3.1.1 Effect of the PEO fragment length on the inclusion process

The structural difference in Brij 56 and Brij 58 is the additional 10 EO units in the latter, so it was expected that a greater number of βCD would be encapsulating this surfactant.

However, the results showed ~7 βCD is interacting with Brij 58. A similar result was obtained for the inclusion of Brij 35, whose structure can accommodate 13 βCD, but only 8 interacted with the surfactant (POPOVA; TOPCHIEVA, 2001).

Despite the similar number of βCD in the complexes formed by Brij 56 and Brij 58, the decrease of the system's enthalpy and entropy was greater for the Brij 58-βCD complex (Table 2.1). Since the stoichiometry of both complexes was similar, the enthalpic and entropic contents related to the desolvation of the surfactant and the βCD cavity, as well as the Brij-βCD interaction, do not vary much from one complex to another. Thus, the difference observed in the thermodynamic parameters is likely due to the conformational changes in the surfactant. The PEO moieties with a greater number of EO units (≥ 18), as in the case of Brij 58, assume a more extended random coil conformation when free in the bulk, while for PEO with short chains, like the one in Brij 56, the structure assumed is dominated by a linear conformation, in which the trans structure is predominant (ZATZ, 1989).

Therefore, the largest decrease of the system's enthalpy and entropy, observed for the Brij 58-βCD complex formation, is due to a significant loss of the PEO random coil conformation, which is less effective for Brij 56. This explains why Brij 58, and also Brij 35, are not filled with βCD since the thread of other molecules would cause a greater conformational change in the surfactant structure, leading probably to a greater decrease in $T\Delta S°$ than in $\Delta H°$, making the formation of complex unfavorable.

3.1.2 Effect of the aliphatic chain length on the inclusion process

The increase of the surfactants' hydrophobicity, by the addition of 2 carbon atoms in the aliphatic chain, had an unexpected effect on the system. The calorimetric experiment involving Brij 76 and Brij 78, that differ from Brij 56 and 58, respectively, by the length of the tail, resulted in a stoichiometry of ~1:20, and ~1:21. Since this number of βCD does not fit in the surfactant's structure, this result may indicate the formation of other structures beyond the host-guest complex, where for each Brij 76 or Brij 78 molecule in this new aggregate, there are 20 or 21 βCD molecules present, respectively.

Various studies have shown the existence of βCD aggregates in solution, as well as their inclusion complexes. For instance, Couto et al. investigated the interaction between native CDs and their hydroxypropyl derivatives with a series of parabens, founding that besides the formation of inclusion complexes, aggregates were being formed. Moreover, the formation of these aggregates was affected by the structure of the parabens: the longer the alkyl side chain,

the grater was the formation of aggregates (methyl < ethyl < propyl < butyl) (COUTO et al., 2019). This behavior can also be observed for the Brij surfactants studied here since the increase in the surfactants' hydrophobicity caused the formation of higher-order complexes.

From calorimetric results alone, it is not possible to determine the structure of these aggregates, that is: (i) the exact stoichiometry of the inclusion complexes present, and (ii) the size of the aggregates. However, from Table 2.1, it is possible to notice that, although the higher stoichiometry values determined for the Brij 76-βCD and Brij 78-βCD, the $\Delta H°$ and $T\Delta S°$ values were similar to the obtained for the formation of the Brij 56-βCD and Brij 58-βCD complexes, respectively. This could indicate that the driving forces responsible for the formation of inclusion complexes with Brij 76 and Brij 78 resemble the ones formed with Brij 56 and Brij 58, and the energy involved in the aggregation process has little contribution to system's enthalpy and entropy change. On the other hand, k_b and, consequently, $\Delta G°$ values were different. For the Brij 78-βCD complex, $\Delta G°$ value was more negative in comparison with the complexes formed with the other surfactants, which can be explained by the 2 additional carbon atoms in the tail, since the longer the aliphatic chain in a surfactant the higher the affinity to βCD (SAINT AMAN; SERVE, 1990). For the complex with Brij 76, however, even with the additional carbon atoms, the stability of the complex was lower than the others. This could be explained by the more hydrophobic feature of this surfactant in relation to the others, causing it to form large self-assembly structures in solution (larger than micelles), as will be shown in the next section, which are probably more stable than the inclusion complexes.

3.2 Size measurements

Given the calorimetric results obtained for the interaction of βCD with Brij 76 and Brij 78, the DLS technique was used for investigating the formation of aggregates in solution. The size measurements obtained for solutions containing βCD, Brij micelles, or both (in the stoichiometric ratio obtained previously by ITC) are shown in Table 2.2.

Table 2.2. Size measurements obtained through DLS for samples containing βCD, Brij micelles, or both (in the stoichiometric ratio), at 298.15 K.

Sample	Size / nm
βCD (2.0 mM)	99 ± 15
Brij 56 (0.24 mM)	81 ± 16
Brij 58 (0.28 mM)	8.4 ± 0.1
Brij 76 (0.10 mM)	89 ± 10
Brij 78 (0.09 mM)	10.7 ± 0.9
Brij 56-βCD (1:8)	80 ± 9
Brij 58-βCD (1:7)	103 ± 4
Brij 76-βCD (1:20)	268 ± 12
Brij 78-βCD (1:21)	191 ± 16

The results obtained for the solutions containing only the βCD indicated the presence of aggregates with 80-120 nm, which is in agreement with De Sousa et al.'s work, where the size distribution for βCD above the CAC (1.60 mM) was 60-120 nm (DE SOUSA et al., 2012). For the solutions containing only the surfactant, the experiments were performed above the cmc, and the results indicated the presence of larger self-assembly structures for the surfactants with 10 EO units (Brij 56 and Brij 76), probably due to their greater hydrophobicity compared to those with 20 EO units (Brij 58 and Brij 78). Finally, for Brij 56 and Brij 58, in the presence of βCD, it was observed structures with ~80 nm and ~100 nm, respectively, which could be related to the βCD aggregates, since the presence of guest molecules might not induce the breaking of these structures (DE SOUSA et al., 2012), or even promote their formation in some cases (COUTO et al., 2019). However, for Brij 76 and Brij 78, in the presence of βCD, the results showed the existence of larger structures with ~270 nm and ~200 nm, respectively, which indicates the formation of aggregates between the host-guest complexes, as proposed by ITC.

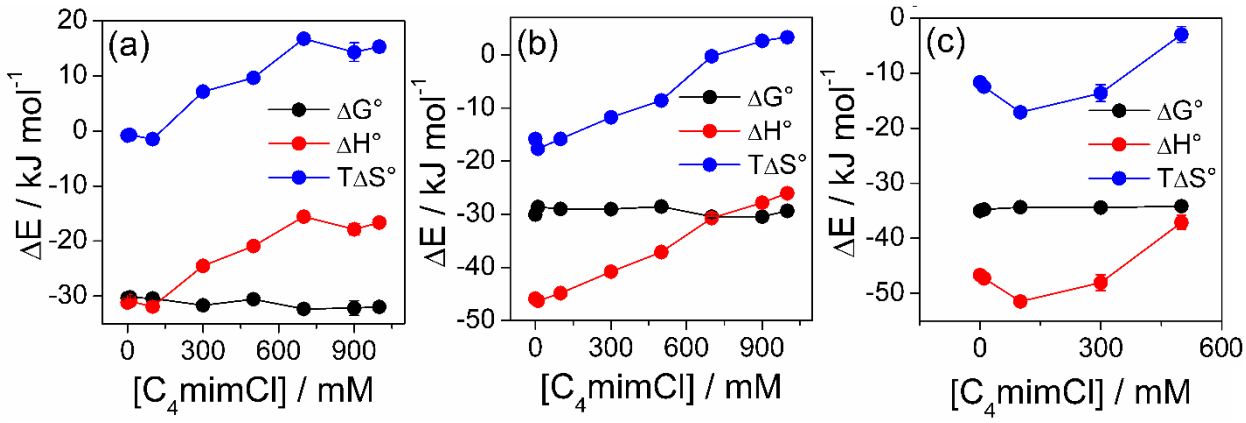
3.3 Effect of C_4mimCl on the interaction Brij-βCD

After the thermodynamic characterization of the interaction between the Brij surfactants and βCD in water, the effect of C_4mimCl on the interaction was studied. Fig. A4 shows the Wiseman isotherms for the interaction of βCD with Brij 56, Brij 58, and Brij 78 in different C_4mimCl concentrations. For Brij 76, the presence of the IL caused the precipitation of the surfactant in all studied concentrations, thus it was not possible to investigate the effect of C_4mimCl on the interaction between this surfactant and βCD. While for Brij 78, the calorimetric

data were obtained for [C_4mimCl] ≤ 500 mM, since for higher concentrations no profile was obtained.

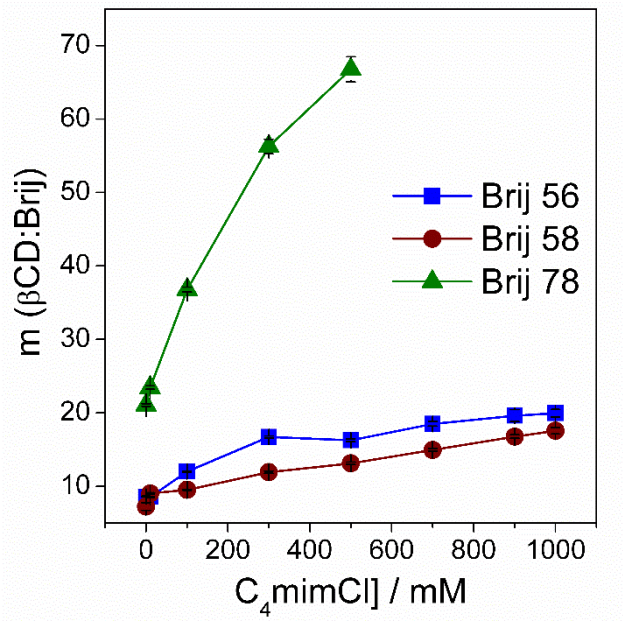
Thus, through adjusting the ITC data to the SSIS model, as showed previously, the thermodynamic parameters were determined and are shown in Fig. 2.5.

Fig. 2.5. Thermodynamic parameters for the interaction between βCD and (a) Brij 56, (b) Brij 58, or (c) Brij 78, in different concentrations of C4mimCl.



The presence of the IL had little influence on the stability of the βCD complexes formed with the three surfactants, as can be seen by the nearly constant values of ΔG° in Figs. 6a-c. However, ΔH° and TΔS° had an overall increase with increasing the C_4mimCl concentration. Moreover, the presence of C_4mimCl promoted the formation of aggregates as indicated by the increase in the stoichiometry (Fig. 2.6).

Fig. 2.6. Stoichiometry (m) of the structures formed by the interaction between βCD and Brij surfactants.



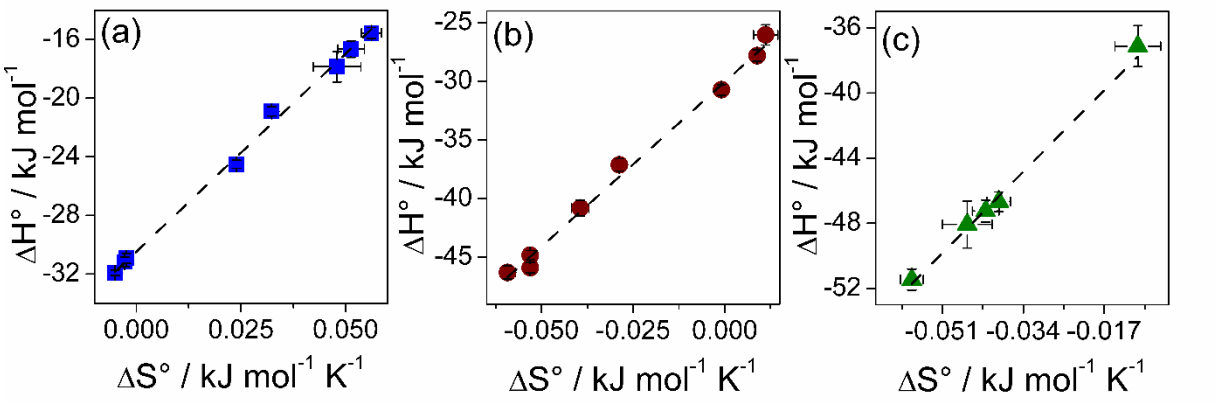
While in water the complexes Brij 56-βCD and Brij 58-βCD didn't self-associate, in a 1000 mM C_4mimCl solution, the stoichiometries of the structures formed were ~1:20 and ~1:17, respectively, indicating the formation of aggregates. For the Brij 78-βCD complexes, which aggregates in water, the presence of the IL promoted further association, reaching a stoichiometry of ~1:67, in 500 mM of C_4mimCl. The aggregation of inclusion complexes induced by the presence of ions was also reported by Lo Notro et. al. The authors investigated the effect of anions from the Hoffmeister series on the formation of pseudopolyrotaxanes between βCD and poly (propylene glycol)-bis-2-aminopropyl ether, founding that the formation and aggregation of the host-guest compounds depend on the anion nature, being more favorable in the order $IO_3^- > SCN^- \approx I^- \approx NO_3^- > HCO_3^- > H_2PO_4^- > Br^- > Cl^- > H_2O > OH^- > F^-$ (LO NOSTRO et al., 2006).

Assuming the hypothesis that the energy involved in the aggregation process has little contribution to the thermodynamic parameters obtained, the increase of $\Delta H°$ and $T\Delta S°$ could be due to the preferential solvation of the βCD and Brij molecules by the IL. The presence of C_4mimCl in the solvation shell makes the water molecules there more structured and, because of that, the surfactants' PEO fragment loses its random coil conformation, and the hydrogen bonding between the water molecules inside the βCD cavity becomes more efficient. Thus, the processes responsible for the decrease of the system's enthalpy and entropy, that is, the PEO conformational change, and the release of water molecules from the βCD cavity, will contribute

less to the ΔH° and TΔS° values. As a result, the higher the IL concentration and presence of C_4mimCl in the solvation shell, the higher the ΔH° and TΔS° values.

Finally, taking into account the behavior shown by the thermodynamic parameters, enthalpy-entropy compensation (EEC) curves were plotted, as shown in Fig. 2.7. The EEC phenomenon is commonly observed in biomolecular recognition (FOX et al., 2018) and self-assembly processes (PAN; RAKSHIT; MOULIK, 2016). It is often related to the changes in the structure of the binding partners and/or modifications in the environment, caused by, for instance, temperature variation (COELHO et al., 2019) or, in this case, the presence of cosolutes.

Fig. 2.7. Plot of ΔH° versus ΔS° for the interaction of (a) Brij 56, (b) Brij 58, and (c) Brij 78 with βCD, in different concentrations of C4mimCl.



The ΔH° versus ΔS° curves obtained showed a highly linear relationship ((a) $R^2 = 0.994$, (b) $R^2 = 0.992$, and (c) $R^2 = 0.990$), highlighting the EEC for the interaction between the Brij surfactants and βCD, in the presence of C_4mimCl. This behavior corroborates to the explanation given for the effect on the thermodynamic parameters, since the increase of ΔH° due to less PEO conformational changes, and release of more structured water molecules from the βCD cavity is accompanied by a compensatory increase of ΔS°. In addition, since ΔH° and TΔS° contribute inversely to the ΔG° value, the stability of the Brij-βCD complexes is not affected by the increase of the C_4mimCl concentration, as shown in Fig. 2.5.

4 Conclusions

Here, the formation thermodynamics of inclusion complexes based on βCD and four nonionic surfactants (Brij 56, Brij 58, Brij 76 and Brij 78), was studied using the ITC technique.

The results showed the inclusion process occurs in both hydrophobic and hydrophilic parts of the surfactants. The complexes' stability depended on the tail and head groups lengths, in which the k_b values followed the order Brij 78 > Brij 58 ≈ Brij 56 > Brij 76, while $\Delta H°$ and $T\Delta S°$ values were negative for all complexes, showing the process is enthalpy-driven. For the more hydrophilic surfactants (Brij 58 and Brij 78), these parameters were more negative due to a greater contribution from the PEO fragment conformational change. As for the more hydrophobic ones (Brij 56 and Brij 76), the ITC and DLS results indicated the self-association of the Brij 76-βCD and Brij 78-βCD complexes, forming aggregates with ~270 nm and ~200 nm, respectively.

In the presence of C_4mimCl, the stability of the complexes remained constant with increasing the IL concentration, while the aggregation of the complexes was promoted. Moreover, a preferential solvation of the interacting molecules by the C_4mimCl caused the increase of $\Delta H°$ and $T\Delta S°$.

Therefore, this study provided valuable knowledge about the interaction between βCD and nonionic surfactants, when the hydrophobic/hydrophilic balance is altered. This information could be of assistant when using these molecules, since the aggregation of the complexes formed by βCD and Brij surfactants can be used in applications, after further investigation.

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FINAL CONSIDERATIONS

Throughout this dissertation, the importance of studying supramolecular systems was extensively shown by the great number of structures and functions this branch of chemistry comprises. The interaction between molecules is present in a variety of biological processes, such as the folding of proteins, formation of DNA and the catalytic action of enzymes, then studying the supramolecular chemistry is also a way to understand how life occurs. However, since the chemistry is always evolving to discover, explain and use systems beyond the ones found in nature, the same occurs to the supramolecules. Over the years, the investigation of compounds formed by the interaction between different molecules (or ions) provided a great amount of knowledge about how host-guest complexes and self-assembly structures are formed, and thus, how they can be applied in new technologies. But, as it was shown here by the complexes formed between β-cyclodextrin and the Brij surfactants, a lot more information can still be extracted from these systems since the number of chemical species present in our world is immense, and so will be the number of supramolecules formed and the knowledge provided by them.

APPENDIX A

Fig. A 1. Calorimetric raw data obtained from the titration of a Brij 58 solution (3.38 mM) in (a) deionized water and in (b) a βCD solution (2.20 mM), at 298.15 K. (c) Plot of ΔH_i versus the molar ratio ($R_{(\text{Brij 58}/\beta\text{CD})}$) for the interaction of Brij

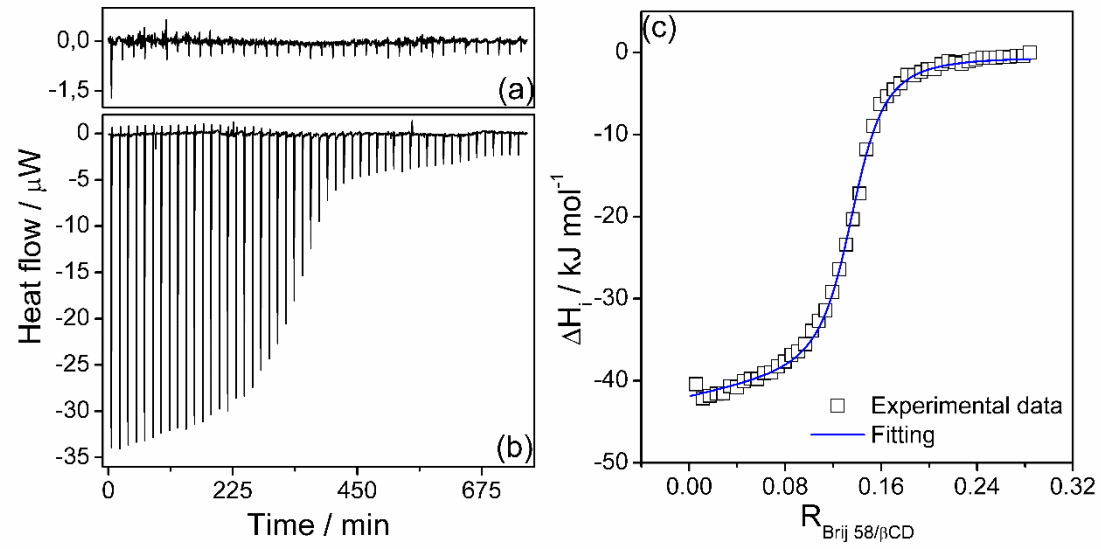

Fig. A 2. Calorimetric raw data obtained from the titration of a Brij 76 solution (2.01 mM) in (a) deionized water and in (b) a βCD solution (2.20 mM), at 298.15 K. (c) Plot of ΔH_i versus the molar ratio ($R_{(\text{Brij 76}/\beta\text{CD})}$) for the interaction of Brij

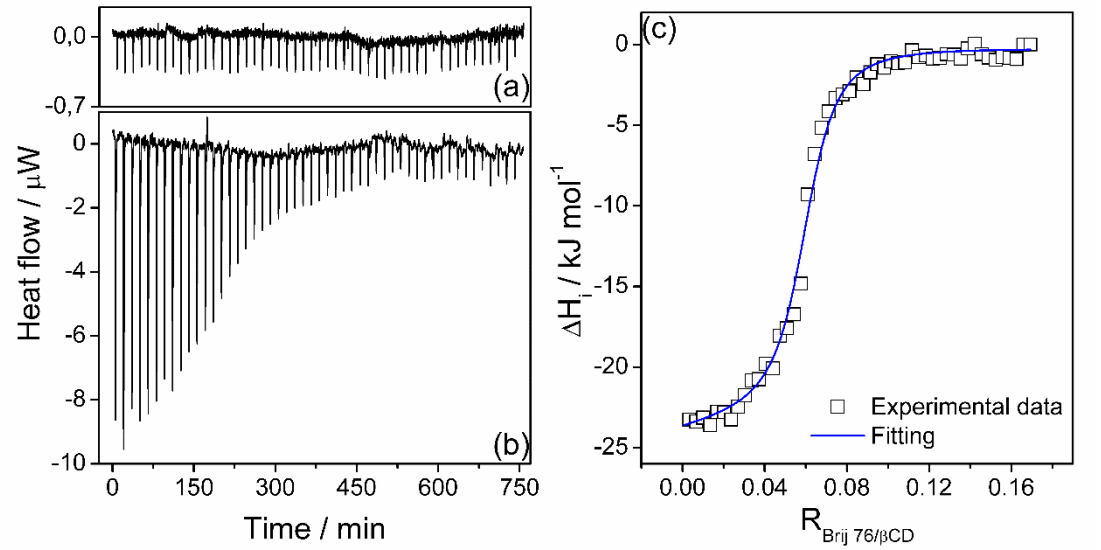

Fig. A 3. Calorimetric raw data obtained from the titration of a Brij 78 solution (1.19 mM) in (a) deionized water and in (b) a βCD solution (2.20 mM), at 298.15 K. (c) Plot of ΔH_i versus the molar ratio ($R_{(Brij\ 78/\beta CD)}$) for the interaction of Brij.

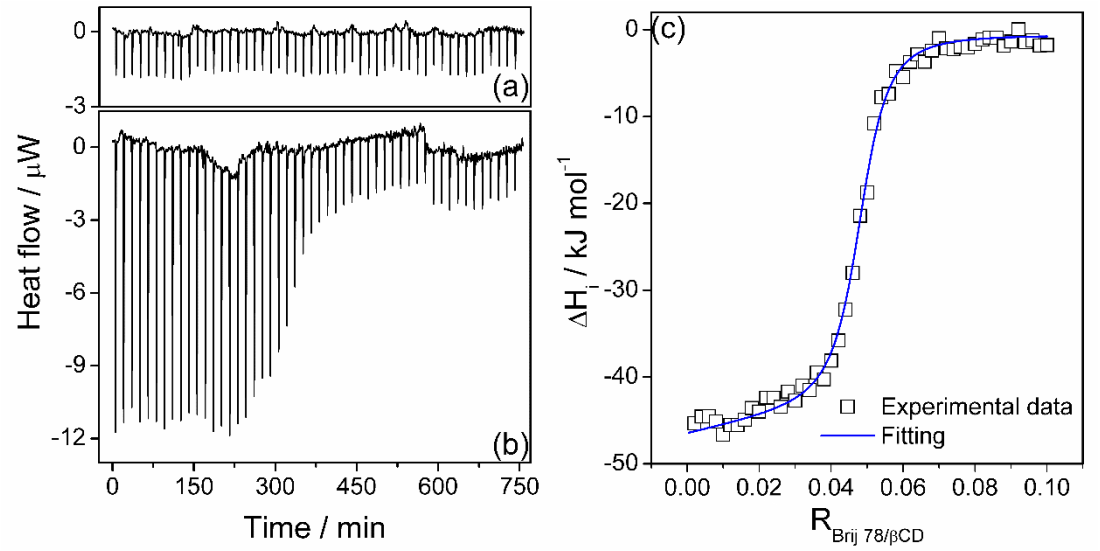

Fig. A 4. Plot of ΔH_i versus the molar ratio ($R_{(Brij/\beta CD)}$) for the interaction of (a) Brij 56, (b) Brij 58, or (c) Brij 78 with βCD, obtained in different concentrations of C4mimCl.