ROMANIAN ACADEMY

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THESIS ABSTRACT

THE STUDY OF THERMODYNAMIC STABILITY OF LIGAND – CYCLODEXTRIN MOLECULAR STRUCTURES. STRUCTURAL AND MORPHOLOGICAL ASPECTS CORRELATED WITH THERMODYNAMIC DATA.

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1. Introduction

"Cyclodextrins are universal molecular recipients for: organic, inorganic and organometallic compounds, neutral, cationic, anionic or even organic radicals" [1]. The main property of cyclodextrins is to form complexes with almost any type of guest molecule. Due to its remarkable molecular architecture, cyclodextrins play an important role in medicine, biology, pharmaceuticals, food and consumer goods, with particular importance being reflected in the number of papers and patents dedicated to cyclodextrin and its inclusion compounds.

In the thesis were made original contributions regarding the thermoanalytic study of some complexes of organic molecules with cyclodextrins and their thermal behavior was correlated with the structural and morphological aspects involved in their formation. In order to support the information derived from the thermodynamic data, quantum chemistry calculations were used to obtain the energy parameters of the complexation interaction and new structural and morphological data were presented in relation to the studied complexes.

The motivation of the study is also related to other aspects, such as:

- the need of new information on the structure, morphology and quantum chemistry calculations for ligand / cyclodextrin systems with biochemical importance;
- the role of energy parameters in highlighting the correlation between the ligand structure and the properties of the complex obtained with cyclodextrin;
- the importance of the studied systems, which can be models within a series of complexes obtained between cyclodextrins and ditopic molecules.

The study in the frame of this thesis is based on the analysis of the results obtained by correlating several experimental methods, namely:

- Thermal analysis and calorimetry methods (Differential Scanning Calorimetry - DSC, thermogravimetric analysis - TG, isothermal titration calorimetry - ITC).
- Structural and morphological characterization methods (Fourier transformed infrared spectroscopy measurements - FT-IR, scanning electron microscopy - SEM, ultraviolet – visible absorption spectroscopy - UV-Vis).
- Determination of pH.
- Quantum chemistry (QC) calculations.

In this study, a series of well-known amino acids and active biochemicals have been selected as guest molecules for which inclusion complexes with different cyclodextrins [**alpha-cyclodextrin (αCD), beta-cyclodextrin (βCD), 2-hydroxypropyl-alpha-cyclodextrin (HPαCD), 2-hydroxypropyl-beta-cyclodextrin (HPβCD), gamma-cyclodextrin (γCD)**] have been synthesized. In the table below are listed the studied systems and the methods of investigation used within this thesis.

Cyclodextrin type / Ligand type	αCD	βCD	2HPαCD	2HPβCD	γCD	Analysis methods
L-Arginine	●	●	●			DSC, TG/DTG, FTIR, SEM,
D-Arginine	●	●	●			DSC, TG/DTG, FTIR, SEM,
L-Histidine	●	●	●			DSC, TG/DTG, FTIR, SEM,
D-Histidine	●	●	●			DSC, TG/DTG, FTIR, SEM,
L-Tryptophan	●	●	●			DSC, TG/DTG, FTIR, SEM,
D- Tryptophan	●	●	●			DSC,TG/DTG, FTIR, SEM,
Uracil	●	●	●	●		DSC, TG/DTG, FTIR, SEM, QC, UV-Vis
5-Fluorouracil	●	●	●	●		DSC, TG/DTG, FTIR, SEM, QC, UV-Vis
Doxorubicin					●	DSC, TG/DTG, ITC, FTIR, SEM, UV-Vis, pH
Cinchonine		●		●	●	DSC,TG/DTG, FTIR, SEM, UV-Vis

Taking into consideration the approached field of study, this thesis aimed to achieve the following specific objectives:

1) Synthesis of inclusion complexes starting from the ligand and the corresponding cyclodextrin, using inexpensive and simple preparation methods.

2) Thermochemical characterization of pure substances from which the synthesis of complexes was started and determination of the corresponding thermochemical parameters.

3) Thermodynamic and thermochemical characterization, stability and essential thermal characteristics of the synthesized complexes using appropriate thermal analysis and calorimetry methods.

4) Spectral analysis in order to check the formation of inclusion complexes.

5) Morphological characterization of the complexes

6) Use of UV-Vis, QC analysis methods for the obtaining of energetic parameters and stoichiometry of complexes.

7) To highlight the influence of the reaction medium and of the component structure on the process of formation of inclusion complexes.

The PhD thesis is structured in 11 Chapters, included in three main parts:

Ist part (chapters 1, 2 3) is devoted to general considerations of phase equilibria thermodynamics in receptor-ligand systems as well as to *the state of the art* of cyclodextrin-inclusion compounds thermodynamics.

IInd part (chapter 4) is dedicated to the experimental methods and techniques involved in sample characterization.

IIIrd part (chapters 5, 6, 7, 8, 9, 10) of the thesis is devoted to the original contributions to the ligand-cyclodextrin systems.

At the end of the thesis are presented the general conclusions and perspectives related to this study, followed by the bibliographic references and the list of scientific articles and communications related to the thesis theme.

Chapter 1 presents a brief introduction that discloses information on the importance of cyclodextrins and inclusion complexes formed with cyclodextrins. The goal/aim, the specific objectives and the structure of the PhD thesis are presented.

Chapter 2 contains essential information related to the thermodynamics of first-order phase transitions. In this chapter are presented fundamental aspects related to the thermodynamic functions of the phase transformations involved in the guest-molecule – cyclodextrin type systems. It is also described based on thermodynamic equations approach, the theory applied in determining the purity of substances.

Chapter 3 contains generalities on the structure and properties of cyclodextrins, as well as the description of the most commonly methods in preparing inclusion compounds. This chapter provides the main information about driving forces and steric factors that influence the structure and thermodynamics of the complexation process.

Chapter 4 presents the equipments and analysis methods involved in this thesis to study pure components and synthesized complexes.

Chapter 5 contains the thermal analysis data obtained for pure cyclodextrins (αCD, βCD, HPαCD, HPβCD, γCD). The characterization of pure cyclodextrins is imperiously needed in order to evaluate the properties of CDs before preparing the complexes, as well as to analyze their formation.

Chapter 6 presents the original contributions resulted from the investigation of inclusion complexes between the uracil or 5-fluorouracil guest molecules and cyclodextrines. There are 16 systems synthesized that were thermodynamically investigated using DSC / TG. The complexation process was validated by the FTIR and SEM methods. The stoichiometry of the complexes was determined before obtaining the solid powders, and quantum chemistry calculations were performed to provide the energetic parameters characteristic for the complexation interaction.

Chapter 7 includes experimental data on the solid state study of complexes formed between the optical isomers of amino acids: arginine, histidine and tryptophan with cyclodextrins. Thermodynamic parameters of pure amino acids and complexes were established by thermal

analysis. Comparative discussions on the complexes stability were performed. FTIR and morphology data for all studied complexes and for the corresponding pure amino acids were provided. Taking into account the obtained data, the influence of the various factors that determined the thermodynamics of the complexation and the structure of the complexes was discussed.

Chapter 8 presents the study of inclusion complexes between cinchonine and cyclodextrins for molar ratios 1: 1, 2: 1 and 1: 2 (ligand-cyclodextrin). Based on thermal analysis data the thermograms and the parameters corresponding to the thermal effects were provided and the stability of the complexes was discussed, the thermochemical data being supported by the structural and morphological analysis. Influence of structural factors and of the reaction medium on the complexity behavior were correlated.

Chapter 9 contains the original contributions resulting from the analysis of the complex formed between doxorubicin and γ-cyclodextrin, in solid and liquid state. The stoichiometry of the solution was investigated and the thermodynamic parameters were determined by isothermal calorimetric titration and UV-Vis spectroscopy data. The solid powder of the complex was investigated by thermal analysis and the corresponding thermograms and thermochemical parameters were presented. Based on the FTIR spectroscopy data, the complexation porcess was evaluated. The morphological analysis was also presented.

Chapter 10 and 11 outline the final conclusions and prospects for expanding and continuing research.

Original contributions to the characterization of ligand-cyclodextrin type systems

2. Comparative study of the inclusion compounds of uracil and 5-fluorouracil with cyclodextrins

The preparation of solid state inclusion compounds (U/αCD, 5FU/αCD, U/βCD, 5FU/βCD, U/HPαCD, 5FU/HPαCD, U/HPβCD, 5FU/HPβCD) was done by "melting in solution" method, using 1:1 molar ratios of ligand-CD. The system stoichiometry was determined by the continuous variation method. Each system was equilibrated 24h, after that the absorbance variation was observed at 258nm for U systems and at 265nm for 5FU formed systems respectively. In this

experiment, stoichiometry was determined for 10^{-5} M aqueous solution and for each of the studied systems, the stoichiometric ratio was 1:1.

These determinations were necessary to verify if the stoichiometry of the diluted aqueous solution correspond to the molar ratio of the systems

DSC thermograms of complexes formed between 5FU or U with cyclodextrins show no presence of thermal process attributed to the melting of the ligand in presence of CD, thus for all the studied complexes the existence of strong interactions between the guest molecule and the CD cavity took places, as indicated in Fig. 2.1.

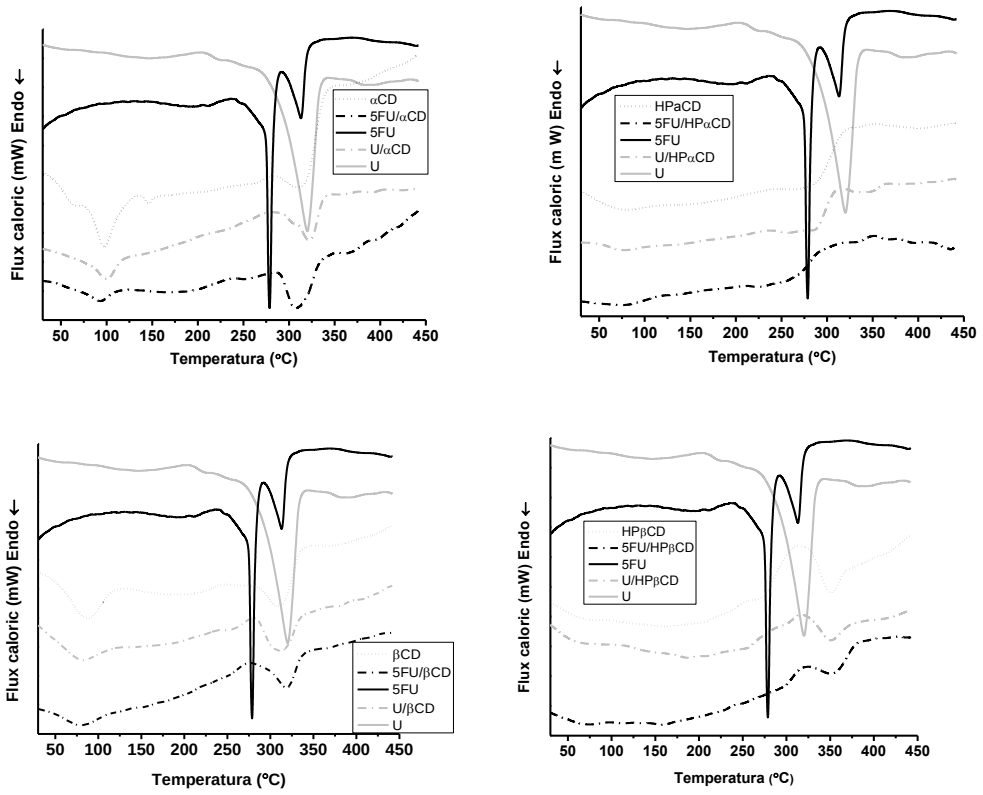

Fig. 2.1 DSC thermograms for U, 5FU, αCD, βCD, HPαCD, HPβCD and synthesized inclusion compounds.

Formation of complexes with functionalised cyclodextrins was more effective than formation of complexes with native cyclodextrins, and this aspect could be highlighted by following the decomposition temperature of the complexes, as shown in Table 2 - 1.

Tabelul 2 - 1

The order of decreasing the decomposition temperature of the inclusion complexes formed between U/5FU and cyclodextrins

Complex	5FU/HPβCD>5FU/HPαCD>U/HPβCD>U/HPαCD>5FU/βCD>U/βCD>5FU/αCD>UαCD							
T (°C)	299.2	262.1	260.7	258.7	254.1	253.2	252.1	239.4

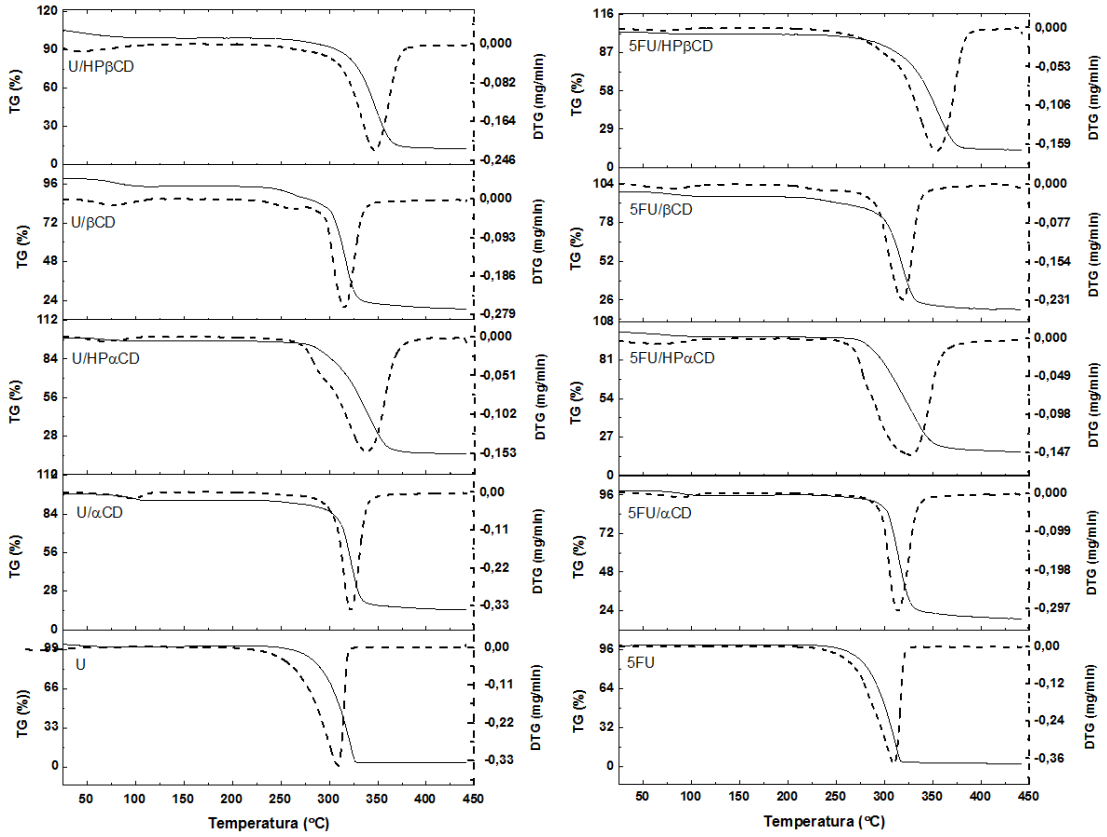

Fig. 2.2 TG curves (continuous line) and DTG (dotted line) for U, 5FU and for complexes formed between U, 5FU and cyclodextrins.

The formation of inclusion complexes for all studied systems took places and the analysis of TG/DTG data (Figure 2.2) confirms the results obtained by DSC [2].

Fig. 2.3 shows FTIR-ATR spectra for U, 5FU, cyclodextrins and inclusion compounds. For pure cyclodextrins, broadband present in the spectrum with the maximum absorption at 3288 cm^{-1} for αCD, 3314 cm^{-1} for βCD, 3302 cm^{-1} for HPαCD and 3330 cm^{-1} for HPβCD is characteristic.

This band is attributed to the O-H stretching vibration in symmetric and anti-symmetric modes and is affected when the inclusion complex was formed [3]. For the 5FU/αCD, U/αCD, 5FU/HPαCD and U/HPαCD systems there are no significant band changes at approximately 3300 cm^{-1}. This band is shifted much more for the complexes 5FU/HPβCDCD, U/HPβCD, U/βCD and 5FU/βCD; it can be said that ligand inclusion occurs with the involvement of a larger number of hydrogen bonds [4].

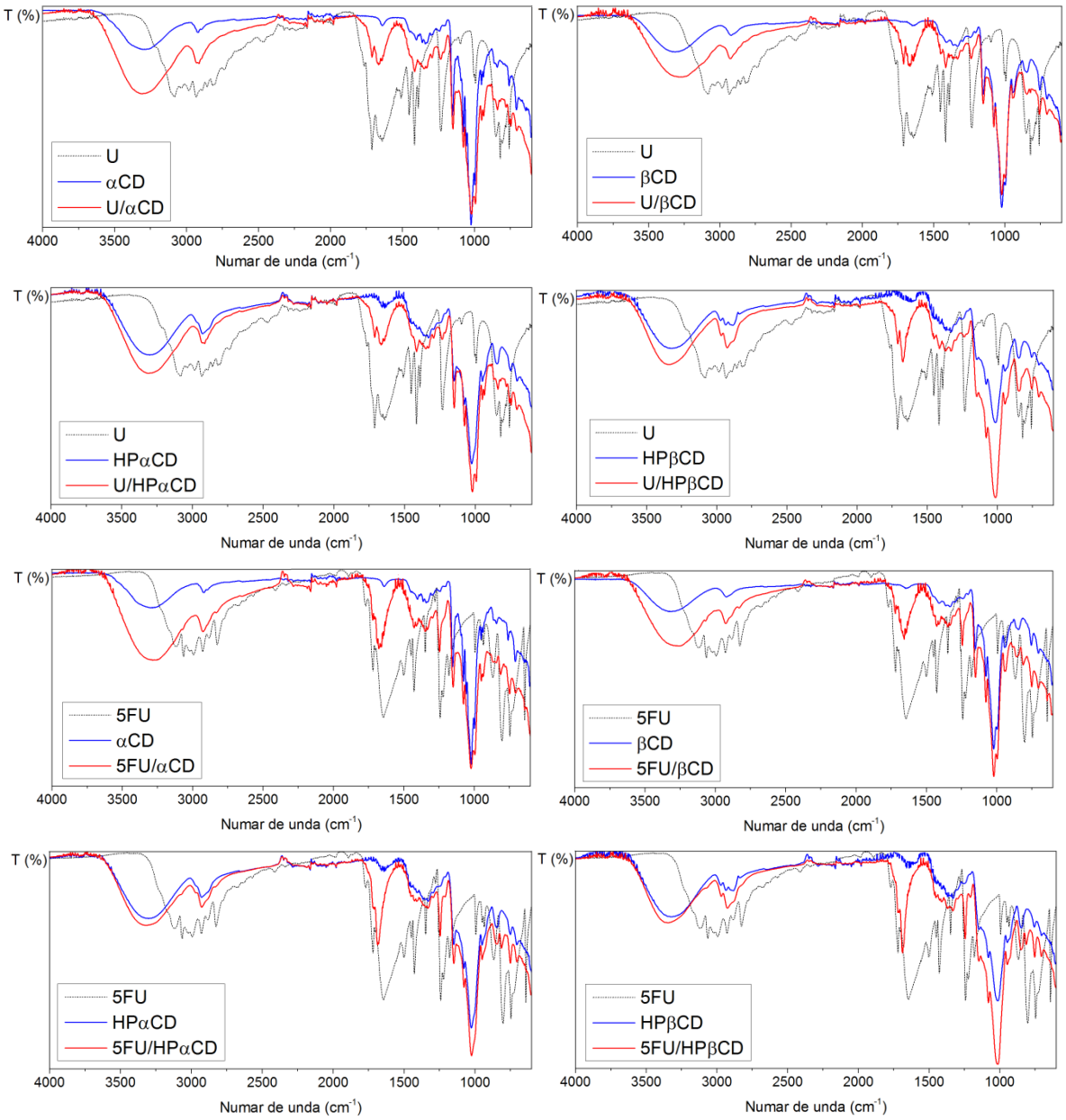

Fig. 2.3 FT-IR spectra for: U, 5FU, cyclodextrins and inclusion compounds formulated for 1: 1 molar ratio (ligand/CD).

Quantum chemistry (QC) calculations were performed using the GAMESS software package facilities installed on an IBM cluster of 65 computing units. The studied systems geometries were optimized by using enhanced wave function sets: STO-3G, STO-6G, n311-6G, and finally, zeta triple valence (TZV) function [5, 6]. Quantum chemistry calculations have shown that the results obtained by applying DFT (density functional theory) confirm that inclusion complexes have been formed between the considered ligands (U/5FU) and the cyclodextrins αCD, βCD, HPαCD, HPβCD.

MPE energies (MPE = reciprocal distortion energy) are represented for the position of the guest molecule inside the CD cavity, for all HG structures (CD/ligand) - Fig. 2.4. In Fig. 2.5, it was observed for the R-configurations (the ligand molecule placed in the center of the small opening of the CD parallel to it), that the plane of the 5FU molecule remained perpendicular to the Oz axis, thus the molecule 5FU was strongly bound to the host molecule by hydrogen bonds (Fig. 2.5).

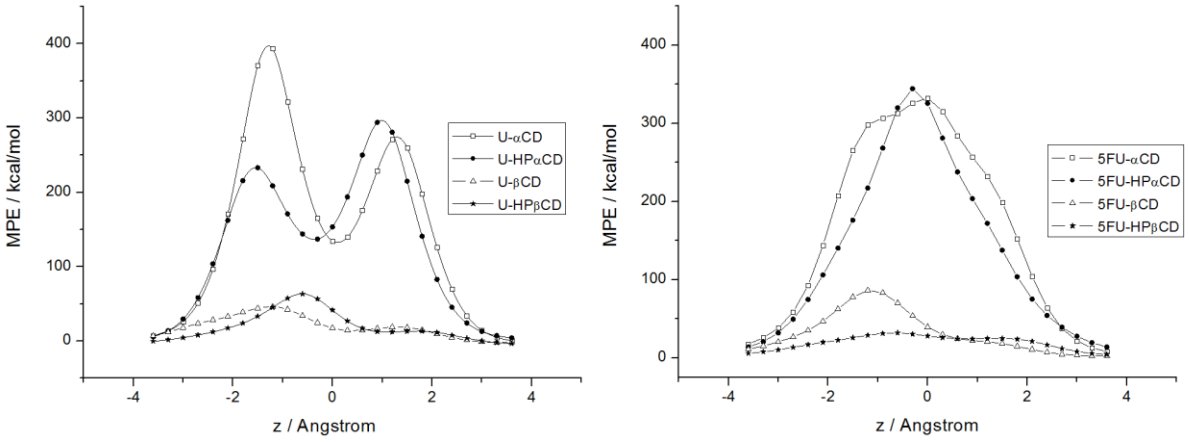

Fig. 2.4 The variation of MPE corresponding to the position of the guest molecule inside the CD cavity for the HG assembly formed between: (left) - the U molecule with αCD, βCD, HPαCD, HPβCD and (right) - the 5FU molecule with αCD, βCD, HPαCD, HPβCD

In the case of H-5FU-R complexes, it can be seen (Figure 2.4) that MPE (Mutual Disturbance Energy) energies are significantly higher for HPαCD and HPβCD. It can be argued that 5FU forms more stable complexes with modified cyclodextrins than with native ones.

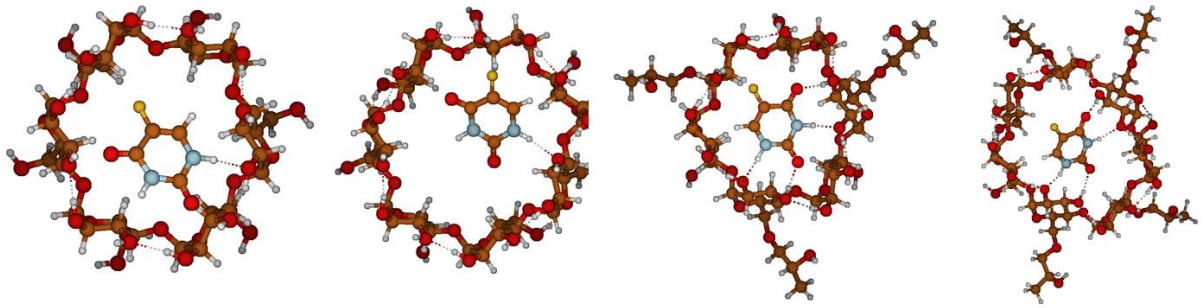

Fig. 2.5 The final configurations of the H-5FU-R inclusion complexes: a) αCD-5FU-R, b) βCD-5FU-R, c) HPαCD-5FU-R, d) HPβCD-5FU-R

Based on the obtained results, it was found that:

- Both U and 5FU molecules interact weaker with αCD, and U molecule interacts weaker than 5FU molecule with HPβCD and βCD cyclodextrins.
- FTIR and DSC/TG data suggest inclusion complex formation of all synthesized samples, indicating the existence of interactions between the constituent molecules of the inclusion complex.
- Considering calculated energies, QC results indicate higher stability for complexes of 5FU with modified cyclodextrins than for complexes of 5FU with native cyclodextrins. The QC calculations agreed with the results indicated by DSC analysis.

3. Cyclodextrin inclusion compounds with L- and D- alpha-amino acids stereoisomers

The complexation process between the optical isomers of the amino acids Arg, His and Trp with αCD, βCD, HPaCD in the solid state was evaluated. It was performed for the first time a systematic analytical study of this type of complexes prepared in 1:1 molar ratio by the co-precipitation method [7]. Thermal analysis data showed that LArg/βCD, DArg/βCD, LHis/βCD, LTrp/βCD and DTrp/βCD are the most thermally stable. In the case of the complexes: LArg/αCD, LArg/HPαCD, DArg/HPαCD, LHis/αCD, LHis/HPaCD, DHis/αCD, DHis/HPaCD, DHis/βCD, LTrp/HPaCD have been made illustrations showing the variation of the starting (T_{on}), transition (T_m) and enthalpy (ΔH) temperatures corresponding to the melting endotherm (Figures 3.1, 3.2 and 3.3). Thus, comparisons could be made between these inclusion complexes. The complex with the highest

thermal stability could be determined, considering as criteria the lowest value of Δ*H* and the highest transition temperature.

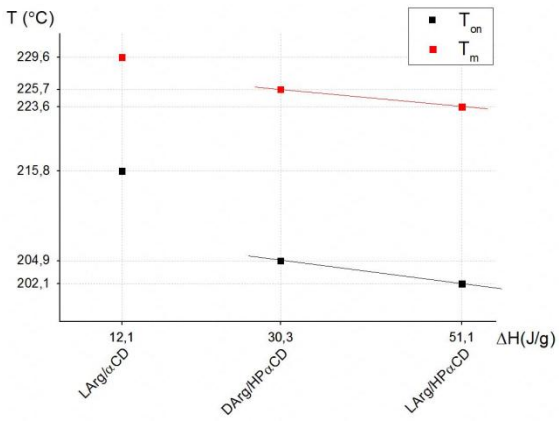

Fig. 3.1 Variation of onset temperature, transition temperature and enthalpy for the melting endotherm of LArg/αCD, DArg/αCD, LArg/HPαCD

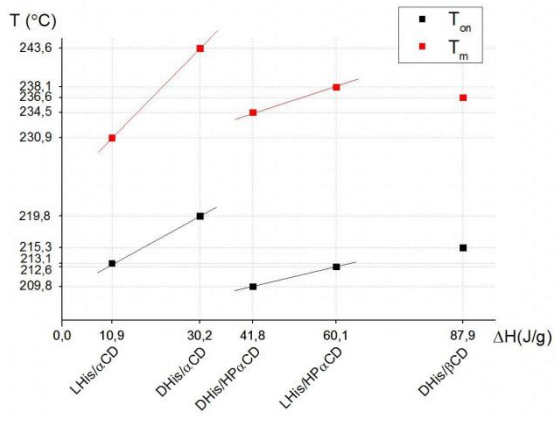

Fig. 3.2 Variation of onset temperature, transition temperature and enthalpy for the melting endotherm of complexes formed between His isomers and αCD, HPαCD and for DHis/βCD complex

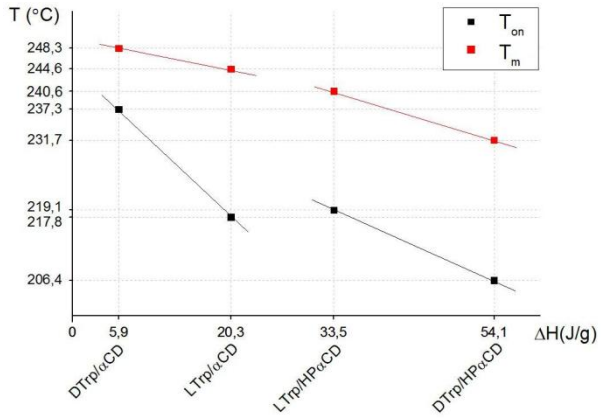

Fig. 3.3 Variation of onset temperature, transition temperature and enthalpy for the melting endotherm of complexes formed between Trp isomers and αCD, HPαCD

Considering for the studied systems the correlation of the resulted data, the following were found:

1) in the case of His, a higher affinity of cyclodextrins for the levogir isomer is observed;

2) in the case of Arg, both isomers are preferred with higher affinity than native cyclodextrins;

3) the most stable inclusion compounds are obtained between the Trp and αCD isomers, βCD, HPαCD, and the most energetically favored ones are those formed with native cyclodextrins.

4) it can be concluded that the amino acids Arg, His and Trp interact with αCD, βCD more strongly than with HPαCD.

4. The study of interaction between cinchonine and cyclodextrins

Solid form complexes formed between Cinc and cyclodextrins: βCD, HPβCD, γCD for molar ratios 1:1, 2:1 and 1:2 were synthesized by co-precipitation method using a mixed water solution of alcohol 50% Vol.

The differences regarding the thermal behavior of systems formed between Cinc and native βCD and γCD cyclodextrins, are shown in Fig. 4.1.

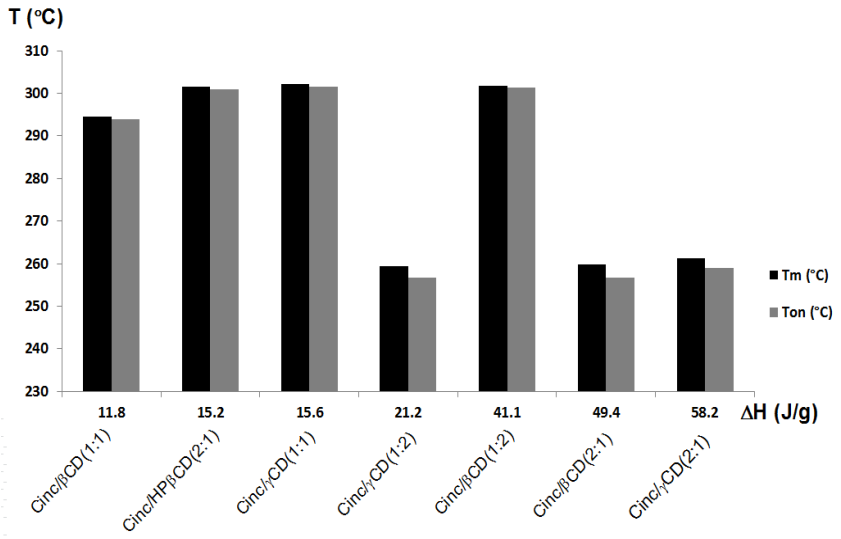

Fig. 4.1 Variation of onset temperature, transition temperature and enthalpy for the melting endotherm of complexes formed between Cinc and cyclodextrins considering the molar ratios of 1:1, 2:1 and 1:2 (guest:host)

DSC/TG analysis of the compounds formed between Cinc and HPβCD showed the formation of the complexes by partial inclusion of Cinc molecule into HPβCD cavity, for the 1:1 and 1: 2 molar ratios (guest: host), (presented in Fig. 4.2 and 4.3).

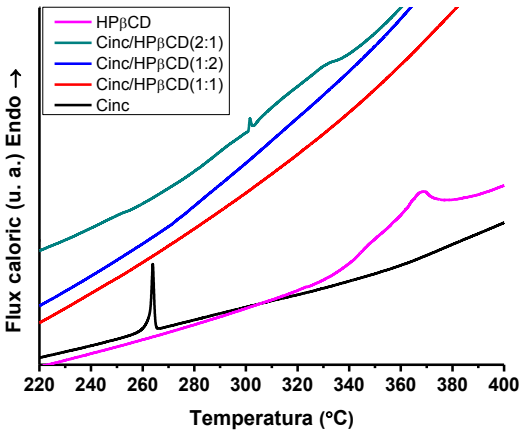

Fig. 4.2 DSC curves for pure Cinc, HPβCD and inclusion complexes formed from different molar ratios.

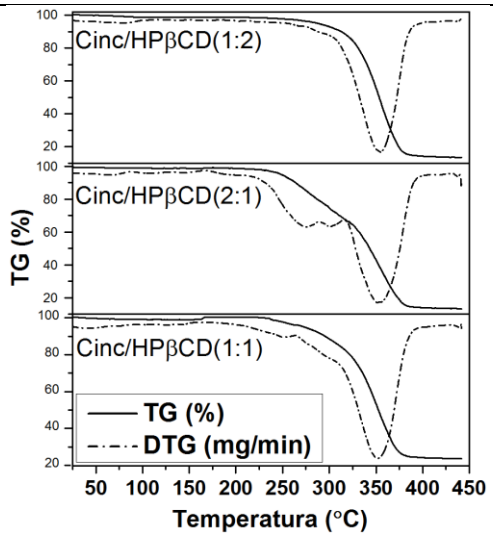

Fig. 4.3 TG/DTG curves for inclusion complexes between Cinc and HPβCD for different molar ratios

Based on thermal analysis data, it was found that:

• There is a possibility of favorable energy interactions between the components of Cinc systems and native cyclodextrins: βCD and γCD, for the 1:1 and 1:2 molar ratios (guest:host), and for Cinc/HPβCD(2:1), by partially inclusion of the two Cinc molecules into the HPβCD cavity.

• The physical size of the CD cavity, the solvent and the CD rim functionalization influence the formation of inclusion complexes.

5. Study of interaction between doxorubicin hydrochloride (Dox) and γ-cyclodextrin

The complexation process between Dox and γCD in the liquid and solid state was evaluated, performing for the first time a systematic thermodynamic study of this interaction.

The non-covalent interaction between Dox and γCD was evaluated in the liquid state using pH measurements, UV-Vis spectroscopy and ITC measurements.

The pH of each Dox/γCD molar ratio was monitored when the complex stoechiometry was evaluated by the continuous variation method and the results are shown in Fig. 5.1.

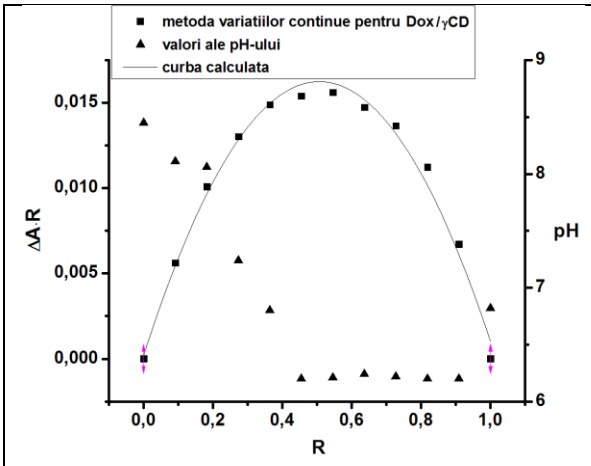

Fig. 5.1 Stoechiometry determination by the continuous variation method for the Dox/γCD system at 25 ° C (λ = 473 nm).

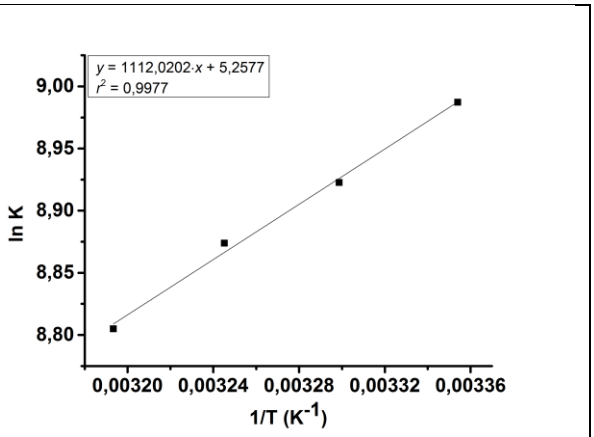

Fig. 5.2 Variation of temperature equilibrium constant for Dox/γCD system.

The results showed for Dox/γCD inclusion complex the 1:1 stoichiometry. The data on the thermodynamic processes that took place in the liquid state confirmed that the interaction was

thermodynamically favorable having a negative variation of Gibbs free energy. It was highlighted that the complexation process is predominantly driven by entropy and moderately driven by enthalpy, this was resulted from van't Hoff analysis based on UV-Vis data and ITC measurements (Figures 5.2 and 5.3).

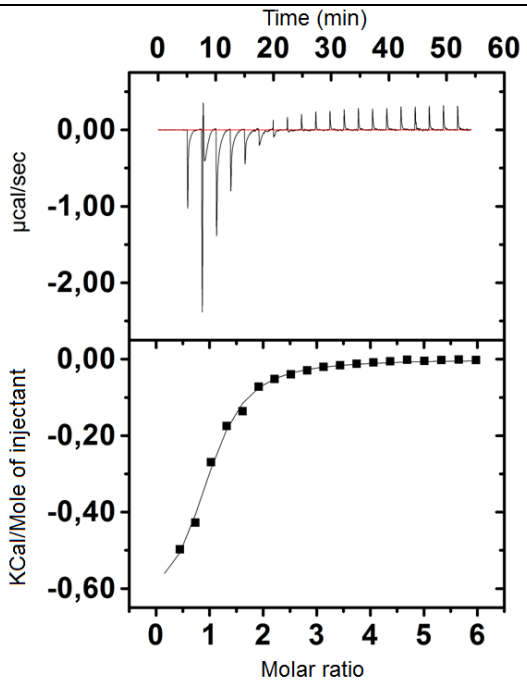

Fig. 5.3 ITC data obtained for the binding interaction between Dox (40.4 mM) and γCD (1.01 mM) in aqueous solution at 25 ° C (p = 0.1 MPa). The upper panel shows gross ITC data. The lower panel shows the integrated and normalized data for the representation of heat values according to the molar ratio, and the continuous line represents the least squares estimated curve.

The TG/DTG analysis of pure and Dox/γCD complexes was performed in the temperature range from 25 °C to 450 °C, and the resulting curves are shown in Fig. 5.4 and 5.5.

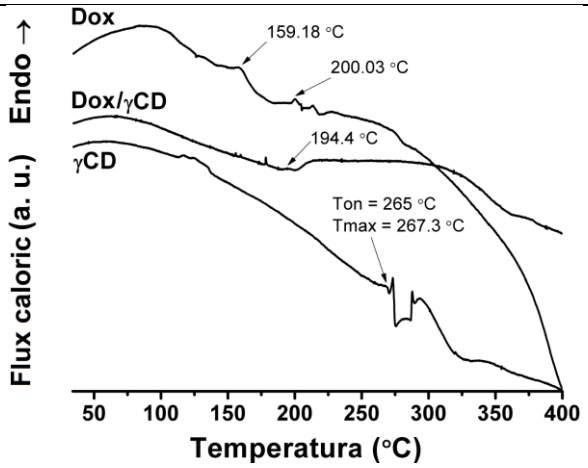

Fig. 5.4 Curbele DSC pentru substanțele pure și pentru complexul de incluziune

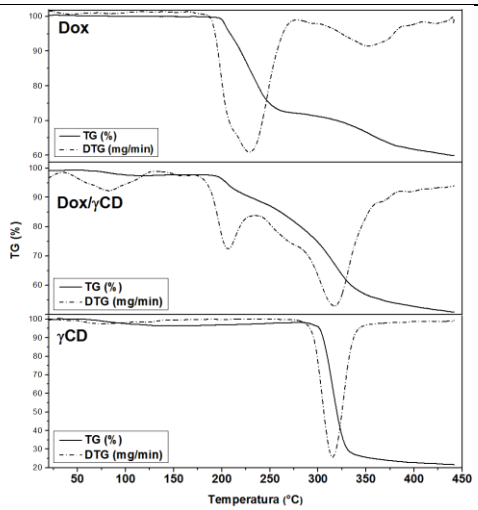

Fig. 5.5 Curbele TG si DTG (inset) pentru substanțele pure și pentru complexul Dox/γCD

The thermal behavior of the Dox/γCD complex is presented in the DSC/TG thermograms of Fig. 5.4 and 5.5. In the temperature range from 25 °C to 130 °C, the dehydration process takes place in three successive steps with a total mass loss of 2.6%. After the dehydration phenomenon, Dox/γCD presents a sequential decomposition process, as evidenced by the DTG profile asymmetry (inserted in Fig. 5.5) [8].

The morphology of pure compounds as well as the Dox/γCD complex were evaluated using SEM, and the obtained images are shown in Fig. 5.6.

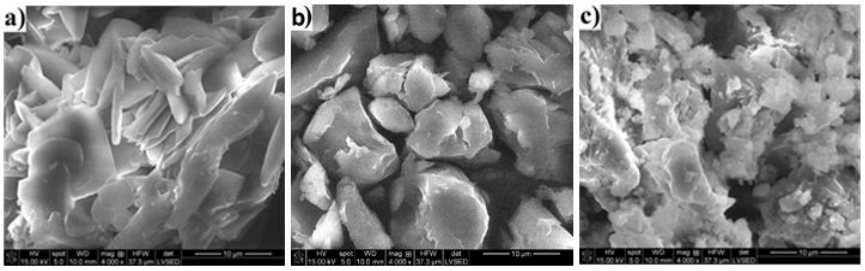

Fig. 5.6 SEM images obtained at 25 ± 1 ° C for: a) Dox, b) Dox/γCD inclusion complex and c) γCD.

It can be observed that the morphology of the Dox/γCD complex presents a new solid phase with no presence of the morphological characteristics of Dox or γCD.

6. General Conclusions. Original contributions

The aim of the thesis is the thermoanalytical study of complexes of cyclodextrins and the correlation of the thermodynamic behavior with the structural and morphological aspects involved in their formation.

In the thesis, characterization of ligand-CD systems was performed by differential dynamic calorimetry, thermogravimetry, isothermal calorimetry titration, and the results were supported by spectral and morphological data.

In this work, the synthesis of inclusion complexes was accomplished by "melting and solution" and "coprecipitation" methods, starting from the 1: 1 molar ratio.

Ligands were chosen to belong to different structural classes to investigate complexation behavior under the influence of various factors such as: molar ratio, synthesis mode, solubility.
The objectives proposed in this paper led to the following conclusions and original contributions:

- In this thesis a systematic thermoanalytic study of the solid powders of the complexes formed between the ligands: uracil (U), 5-fluorouracil (5FU) and cyclodextrins: αCD, HPαCD, βCD și HPβCD, were done. The resulted values of the decomposition temperatures of the complexes were used in order to evaluate the stability.
- Quantum chemistry calculations were done for systems formed between U, 5FU and cyclodextrins: αCD, βCD, HPαCD, HPβCD. The values of the binding, deformation and mutual perturbation energy values were established by DFT calculations.
- The investigation of systems formed between optical isomers of amino acids: arginine (Arg), histidine (His), tryptophan (Trp) wih cyclodextrins: αCD, βCD, HPαCD was accomplished. The experimental results related to thermal, spectral and morphological behavior solid powders of the complexes formed between His, Arg and cyclodextrins, were reported. Comparative issues of the isomers of amino acids considered with cyclodextrins have been discussed considering the contribution of driving forces of the complexation process.
- It was shown that native cyclodextrins αCD and βCD interact strongly with amino acids than HPαCD. Based on the obtained data, it was found that the size of the CD cavity and the existence of the functionalization of CD cavity can acting as chiral selectors for the optical isomers of amino acids.

- The influence of structural factors on the thermodynamic behavior was discussed for the first time and the corresponding energetic parameters were specified for both the aqueous solution and solid powder complex formed between doxorubicin (Dox) and γCD (Dox/γCD). For a 10^{-5} M aqueous solution of Dox and γCD, the stoichiometry was found to be 1:1. In solid state, FTIR and SEM thermal data confirm that the Dox/γCD complex was formed by partial inclusion of the Dox molecule in the γCD cavity.
- For the first time, the complexes formed between cinconin (Cinc) and cyclodextrins were investigated in solid state and it was shown that the presence of the cosolvent influences the complexation process. Thus, the thermal analysis data and FTIR results showed the existence of interactions between the components without inclusion of Cinc in the CD cavity for systems formed between Cinc and native cyclodextrins, considering the molar ratios of 1:1 and 1:2. An important role is played by CD functionalization, justifying for Cinc/HPβCD the posibility to form both the 1:1 molar ratio complex and also the 1: 2 molar ratio complex.
- In the case of ligand molecules (Cinc and Dox) made up of two structural units, it was observed that for the 1:1 molar ratio (in the solid state), a partial inclusion of the ligand molecule in the γCD cavity was happend.
- Based on the thermodynamic parameters obtained from the DSC, comparative diagrams were done considering the variation of onset temperature, transition temperature and enthalpy for the melting endotherm of the complexes formed without inclusions into CD cavity of the guest molecule (systems formed between Cinc or optical isomers of the amino acids with cyclodextrins). It was shown there is a tendency that the lowest enthalpy values correspond to the highest values of the start and transition temperature of the melting endotherm. This can be considered as a selection criterion for the determination of stability within the same set of complexes formed without inclusion of guest.
- The importance of the driving forces in the complexation process, such as: hydration, presence of cosolvent, the possibility of self-assembly, the size and functionalization of CD cavity and the structural characteristics of the ligand molecule were discussed.
- It was emphasized that the diluted aqueous solutions used in synthesis of the complexes determined a 1:1 stoichiometry of the complexes formed between cyclodextrins and the ligands: Dox, Cinc, U and 5FU.

- In this thesis the SEM images corresponding to inclusion complexes formed between the considered ligands and cyclodextrins were analyzed for the first time.
- In this work, the importance of characterization of pure substances before the synthesis steps is underlined. Considering the thermal analysis of cyclodextrins, it is pointed out that the presence of different thermal behavior can be induced by a series of factors such as: commercial variety, storage time and conditions.
- The results obtained in this thesis emphasize the importance of methods of thermal analysis in the study of complexes formed with cyclodextrins, together with other methods of investigation.

7. Perspectives of expanding and continuing research

The properties of cyclodextrins have led to the development of many research branches, and inclusion complexes formed with cyclodextrins constitute an enormous research area with new perspectives on combinatorial chemistry.

Appreciation of complexity stability and reactivity are important in application development, so data on energy factors are needed in areas such as molecular engineering and supramolecular chemistry.

The scientific data resulting from this study may be starting points for new research such as chiral separation and catalysis, as well as starting points for making realistic models of more complicated processes such as macromolecular hydration, hydrophobic proteins, various types of interaction etc.

The new research will allow experimental measurements to be expanded in terms of the influence of physicochemical factors such as: the concentration of the constituent molecules of the system, the concentration and type of the solvent, the pH, the temperature, complexes stoichiometry control etc.

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