ROMANIAN ACADEMY
"PETRU PONI" INSTITUTE OF MACROMOLECULAR CHEMISTRY

NMR Techniques for Characterization of Cyclodextrins and their Inclusion Complexes

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IAȘI, 2017

ROMANIAN ACADEMY
"PETRU PONI" INSTITUTE OF MACROMOLECULAR CHEMISTRY, IAȘI

Nr 6857 / 10.X.2017

To Mr./Mrs. .....

We would like to inform you that on the **30th of October 2017**, at **12:30 pm**, in the library of the „Petru Poni" Institute of Macromolecular Chemistry from Iași, will be the public presentation of the doctoral thesis entitled **"NMR Techniques for Characterization of Cyclodextrins and their Inclusion Complexes"**, elaborated by **Mihaela Balan (married Balan-Porcărașu)**, in order to obtain the scientific title of Doctor.

The doctoral commission has the following members:

President:

PhD. Anton Airinei, Senior Researcher (CSI), Director of „Petru Poni" Institute of Macromolecular Chemistry from Iași

Scientific Coordinator:

Acad. Bogdan C. Simionescu, Senior Researcher (CSI), „Petru Poni" Institute of Macromolecular Chemistry from Iași

Referees:

Prof. Gabi Drochioiu, "Alexandru Ioan Cuza" University of Iași
PhD. Mircea Bogdan, Senior Researcher (CSI), National Institute for Research and Development of Isotopic and Molecular Technologies, INCDTIM from Cluj-Napoca
PhD. Luminița Marin, Senior Researcher (CSII), „Petru Poni" Institute of Macromolecular Chemistry from Iași

According to the Regulation regarding the organization and conducting the doctorate for obtaining the scientific titles within the Romanian Academy, we are sending you the abstract of the doctoral thesis with the request to communicate in writing your appreciations and remarks.

We invite you to participate to the public defence of the doctoral thesis.

ACADEMIA ROMÂNĂ INSTITUTUL DE CHIMIE MACROMOLECULARĂ "PETRU PONI" IAȘI

Director,
Dr. Anton Airinei

Acknowledgments

I give my sincere thanks to my supervisor, ***Acad. Bogdan C. Simionescu,*** *for his guidance and advice given during my scientific research period.*

Kind thanks and gratitude to ***PhD. Călin Deleanu*** *for his advice and for his implication in forming me as a scientist.*

Thanks to ***PhD. Alina Nicolescu*** *for her advice and for the help she offered me during my research period. Also, I would like to thank her for the knowledge she transmitted to me regarding NMR Spectroscopy and for all the encouragements she has given to me along the years.*

Thanks to the ***Romanian Academy*** *for the financial support.*

Thanks to the Romanian National Authority for Scientific Research - UEFISCDI, for the financial support through the project "Polyrotaxanes based on π Conjugated backbone for Micro/Optoelectronic Applications" (PN-II-ID-PCE-2011-3-0035, January 2012 – November 2016).

Thanks to ***PhD. Anton Airinei***, ***Prof. Gabi Drochioiu***, ***PhD. Mircea Bogdan*** *and* ***PhD. Luminița Marin***, *president and referees of the doctoral commission for analyzing the thesis and for their suggestions.*

Kind thanks to my colleagues form the NMR Laboratory, ***Mihaela***, ***Gabriela***, ***Ana-Maria***, ***Anișoara*** *and* ***Liviu*** *for the moral support, patience and the sympathy they showed during my research period.*

Thanks to all my colleagues from the Physics of Polymers and Polymeric Materials Department and also to all my colleagues from the „Petru Poni" Institute of Macromolecular Chemistry for their advice and for creating a pleasant work environment. I want to thank for collaboration to ***PhD. Aurica Farcaș*** *and* ***PhD. Cristian Peptu*** *and also to all the other colleagues with whom I worked and published articles that are not included in this research.*

Thanks to my friends and my family, especially to my father, my sister and my husband, Sergiu, for their unconditionally support, patience and for the love they showed me during these years.

Table of contents

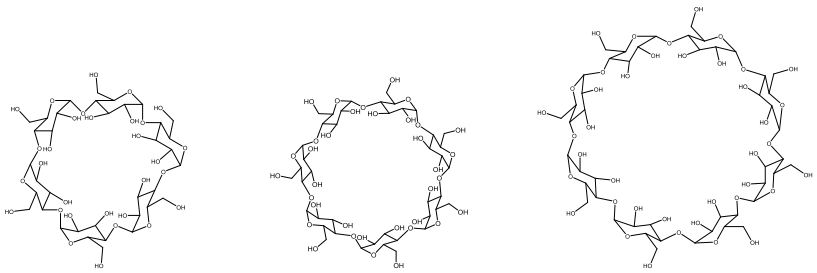
Key words: NMR, cyclodextrins, inclusion complexes, sugars, substituted cyclodextrins benzimidazolium.

***Abbreviations*:**
NMR – Nuclear Magnetic Resonance Spectroscopy
CD – cyclodextrin
NOE –Nuclear Overhauser effect
PCA – Principal Component Analysis
2HPBCD – 2-hydroxypropyl-β-cyclodextrin
MeBCD – methyl-β-cyclodextrin
CD-LA – cyclodextrin esterified with oligolactate
TSP – 3-(Trimethylsilyl)propionic-2,2,3,3-d_4 acid sodium salt
TMS – tetramethylsilane
DBF – 2,7-dibromofluorene

The first part of the thesis has 2 chapters of literature study. **Chapter 1** contains an overview of NMR Spectroscopy including the physical principle of the method, information obtained from spectra and types of experiments. **Chapter 2** deals with cyclodextrins and their inclusion complexes and with the use of NMR Spectroscopy and other methods in their characterization.

The second part contains the original research and it has 4 chapters. **Chapter 3** refers to the NMR characterization of cyclodextrins and quantification of some sugars in complex aqueous matrices. α-, β- and γ-cyclodextrins were characterized in D_2O and DMSO-d_6 solutions. Also, 4 sugars related to cyclodextrins were characterized and cuantified in fruit juices. Other 10 substituted cyclodextrins were characterized in D_2O and DMSO-d_6: sulfobutyl ether-β-cyclodextrin, sodium salt, monochlorotriazynyl-β-cyclodextrin, sodium salt, methyl-β-cyclodextrin, 2-hydroxypropyl-β-cyclodextrin and α-, β- and γ-cyclodextrins substituted with oligolactate residues, for which the position of the substituent was determined to be at the carbon atom number 6 of the glucopyranose unit. This chapter also contains the study on the influence of temperature, pH and presence of internal and external standards on the NMR spectra of cyclodextrins.

One of the study included in this chapter deals with NMR characterization of the three cyclodextrins that are most frequently used for complexation: α-cyclodextrin (**ACD**), β-cyclodextrin (**BCD**) and γ-cyclodextrin (**GCD**). The spectral parameters (chemical shifts, multiplicity and coupling constants) were obtained in D_2O and DMSO-d_6. These two solvents were chosen because of the solubility of the cyclodextrins and their inclusion complexes and because the applications of the complexes. Many complexes have applications in medicine and most of the tests that are specific in the pharmaceutical industry are made in aqueous or dimethylsulphoxide solutions.



α-cyclodextrin (**ACD**) β-cyclodextrin (**BCD**) γ-cyclodextrin (**GCD**)

Cyclodextrins are composed of α-(+)-glucopyranose units in $^4C_1$ conformation. The glucose units are linked by α(1→4)-glycosidic bonds resulting torus shaped macrocycles with an inner cavity.

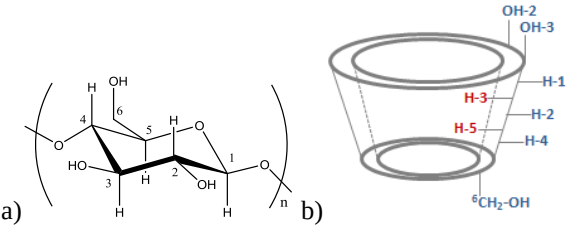
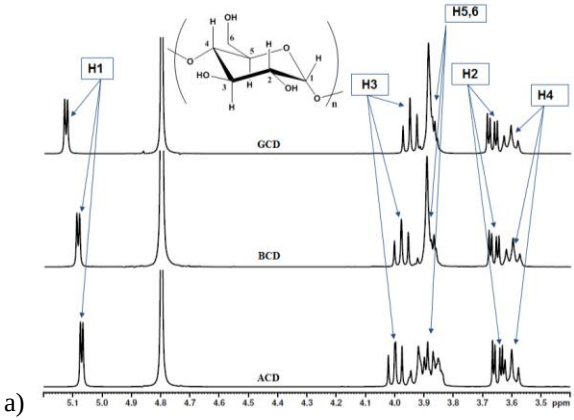
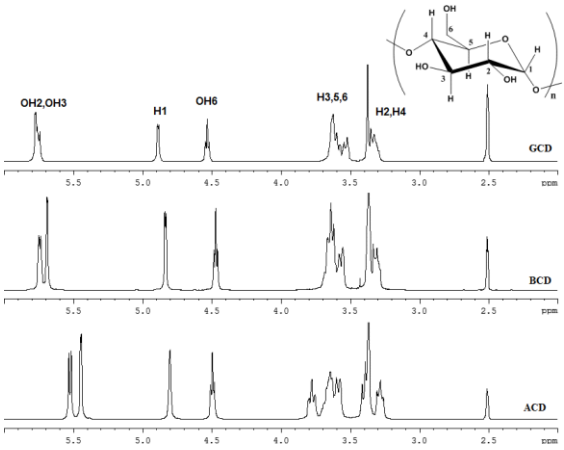


Figure 1. a) Structure of the glucopyanose unit in cyclodextrins and numbering of the carbon atoms; b) schematic representation of cyclodextrins' macrocycle and positioning of the hydrogen atoms

1D and 2D NMR experiments (^{1}H-RMN, ^{13}C-RMN, H,H-COSY, H,C-HMQC, H,C-HMBC and undecoupled H,C-HSQC) were recorded for the three cyclodextrins in D_2O and DMSO-d_6.

In the ^{1}H-NMR spectra we can see isolated peaks for H1, H2, H3 and H4 and H5 and H6 are overlapped. Although the three cyclodextrins have different numbers of glucopyranose units (between 5 and 8) the number of peaks in the ^{1}H-NMR spectra is the same. This particular characteristic is due to the fact that the molecules are symmetric. In the ^{1}H-NMR spectra of the unsubstituted cyclodextrins in D_2O the peaks of the OH groups are not present due to the fast exchange between the labile hydrogens and the deuterium atoms from D_2O. In the ^{1}H-NMR spectra recorded in DMSO-d_6 the peaks for the primary and secondary hydroxylic protons are present.





b)

Figure 2. ^{1}H-NMR spectra for **ACD**, **BCD** and **GCD** in D_2O (a) and DMSO-d_6 (b)

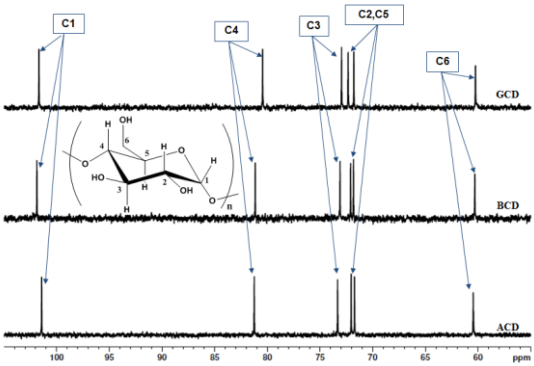


Figure 3. ^{13}C-NMR spectra for **ACD**, **BCD** and **GCD** in D_2O and the assignment of the peaks.

Another study included in this research was the analysis of some cyclodextrin related sugars in complex aqueous matrices (fruit juices). Although NMR is a less sensitive technique it has the advantage that it gives the global profile of a sample. In complex mixtures, by NMR we can observe the presence of unknown or unexpected compounds. Solution NMR spectra for these complex matrices have tens of peaks that overlap. Due to the complexity of the spectra it is almost impossible to attribute every peak from a given spectrum.

Four sugars (glucose, frustose, sucrose and galactose) were quantified in natural and commercial fruit juices.

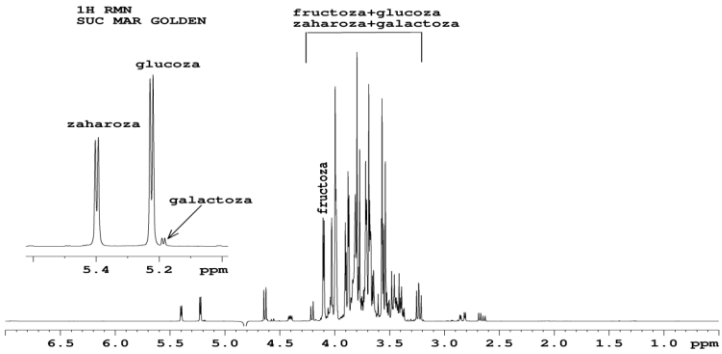


Figure 4. ^{1}H-NMR spectrum for a Golden apple juice sample and the assignment of the peaks for sugars

Another study included in this chapter deals with NMR characterization of modified cyclodextrins. Cyclodextrins can be chemically modified in order to change their solubility and their inclusion preferences. Four modified cyclodextrins were characterized in aqueous solutions (sulfobutyl ether-β-cyclodextrin, sodium salt, monochlorotriazynyl-β-cyclodextrin, sodium salt, methyl-β-cyclodextrin, 2-hydroxypropyl-β-cyclodextrin) and 6 α-, β- and γ-cyclodextrins substituted with oligolactate residues were characterized in DMSO-d_6 solutions. From ^{13}C-NMR spectra and 2D experiments, for the cyclodextrins substituted with oligolactate the preferred position for binding of the substituent was determined to be at carbon 6 of the glucopyranose residue.

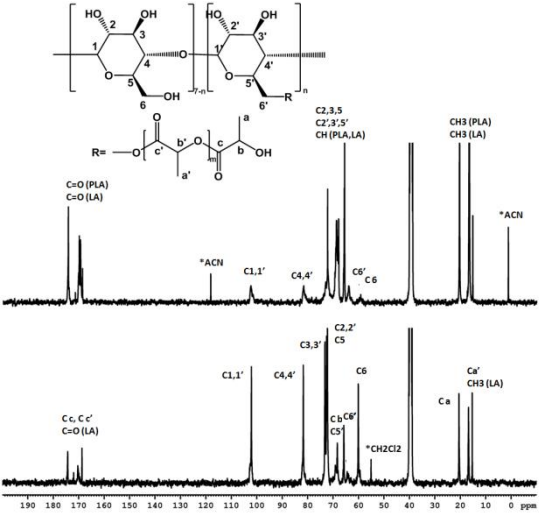


Figure 5. ^{13}C-NMR spectra for **BCD-LA-F2** (up) and **BCD-LA-F1** (down), in DMSO-d_6 and the assignment of the peaks

The influence of some experimental factors (temperature, pH, presence of internal and external standards) on the NMR spectra of cyclodextrins was also studied in this chapter.

Conclusions for chapter 3:

- Three native cyclodextrins (α-, β- and γ-cyclodextrins), 4 cyclodextrin related sugars (glucose, fructose, sucrose, galactose), and 10 chemically modified cyclodextrins (sulfobutyl ether-β-cyclodextrin, sodium salt, monochlorotriazynyl-β-cyclodextrin, sodium salt, methyl-β-cyclodextrin, 2-hydroxypropyl-β-cyclodextrin and α-, β- and γ-cyclodextrins substituted with oligolactate residues) were completely characterized by NMR spectroscopy.

- The four sugars were quantified in complex aqueous matrices (fruit juices) and a statistic PCA model was developed for chemometric separation of the samples.

- In the case of oligolactide substituted cyclodextrins the binding site was determined to be at position 6 of the glucopyranose units.

- The effect of temperature, pH and internal and external standards on the NMR spectra of cyclodextrins were also studied.

Chapter 4 contains a study regarding the complexation between cyclodextrins and halogenated aromatic compounds. The stoichiometry and association constants of the complexes between β-cyclodextrin and three halogenophenols (2-chlorophenol, 4-chlorophenol and 2,4-dichlorophenol) were determined. The stoichiometry of the complexes is 1:1 and the stability of the complexes decreases in the order: 2,4-dichlorophenol>4-chlorophenol>2-chlorophenol.

For example, some of the ^{1}H-NMR spectra recorded for the determination of stoichiometry of the complex between 2,4-dichlorophenol (24DCP) and β-cyclodextrin are presented in figure 6.

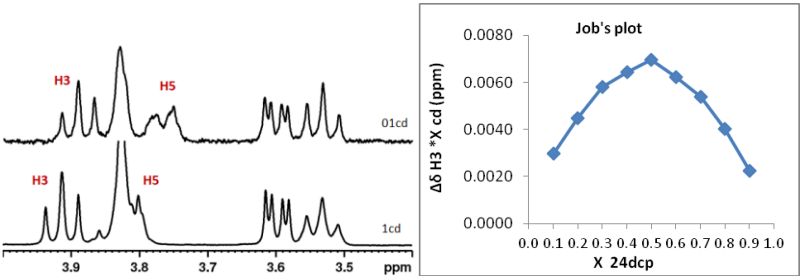


Figure 6. ^{1}H-NMR spectra for 24DCP-BCD in D_2O, detail of the BCD peaks from the spectra of 1cd (C_{BCD}=1 mM and C_{24cp}=0 mM) and 01cd (C_{BCD}=0,1 mM and C_{24cp}=0,9 mM) and Job's Plot with stoichiometry 1:1

This chapter also contained the study on the inclusion of 2,7-dibromoflourene and a polymer derived from it with 3 different macrocycles: totally methylated β-cyclodextrin, partially methylated γ-cyclodextrin and cucurbit[7]uryl. The affinity of 2,7-dibromoflourene and of its polymer is greater for cyclodextrins than for cucurbit[7]uryl.

Conclusions for chapter 4

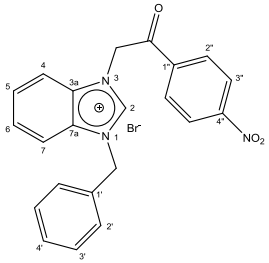
- In the case of the interactions between 2-chlorophenol, 4-chlorophenol and 2,4-dichlorophenol with β-cyclodextrin, the peak for H5 from inside the cyclodextrin cavity is shifted more than the peak for H3. 2,4-dichlorophenol induces the biggest shifts, then 4-chlorophenol and 2-chlorophenol induces the smallest shifts.

- The stoichiometry of the complexes between the three halogenophenols and β-cyclodextrin is 1:1 as determined by continuous variation method.

- The stability of the complexes varies in the order: 4-dichlorophenol>4-chlorophenol>2-chlorophenol.

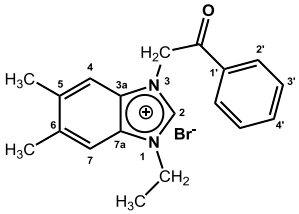
- The affinity of 2,7-dibromoflouren and of its polymer is greater for cyclodextrins than for cucurbit[7]uryl.

Chapter 5 contains results from the characterization of some complexes between cyclodextrins and 1-benzyl-3-[2-(aryl)-2-oxoethyl]-5,6-dimethylbenzimidazolium salts. The preferred inclusion geometry was determined from NMR experiments.



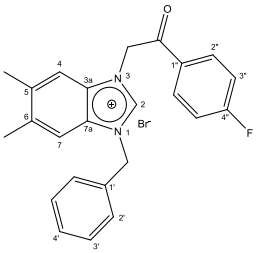
Bz1255

(N-benzyl), N-(4-nitrobenzyl) benzimidazolium bromide



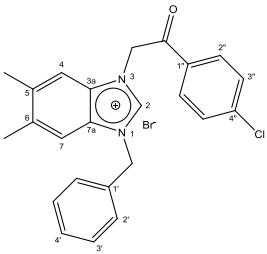
BzB122

1-ethyl-3-[2-phenyl-2-oxoethyl]-5,6-dimethylbenzimidazolium bromide



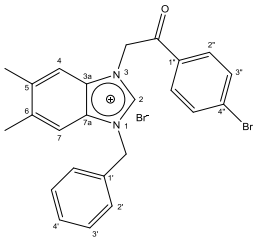
Bz1a

1-benzyl-3-[2-(4-fluorophenyl)-2-oxoethyl]-5,6-dimethylbenzimidazolium bromide



Bz1b

1-benzyl-3-[2-(4-chlororophenyl)-2-oxoethyl]-5,6-dimethylbenzimidazolium bromide



Bz1c

1-benzyl-3-[2-(4-bromophenyl)-2-oxoethyl]-5,6-dimethylbenzimidazolium bromide

For Bz1a-c from the ROESY experiments was determined that the strength of the interactions with α- and β-cyclodextrins depends on the para-phenyl substituent and it varies in the order F<Cl<Br. The cavity of β-cyclodextrin can accommodate the substituent from N1 and the one from N3 while the cavity of α-cyclodextrin can accommodate only the substituent from N3.

Another study was conducted on the complex between Bz1255 and β-cyclodextrin. From the ROESY experiment resulted that there are more possible inclusion geometries:

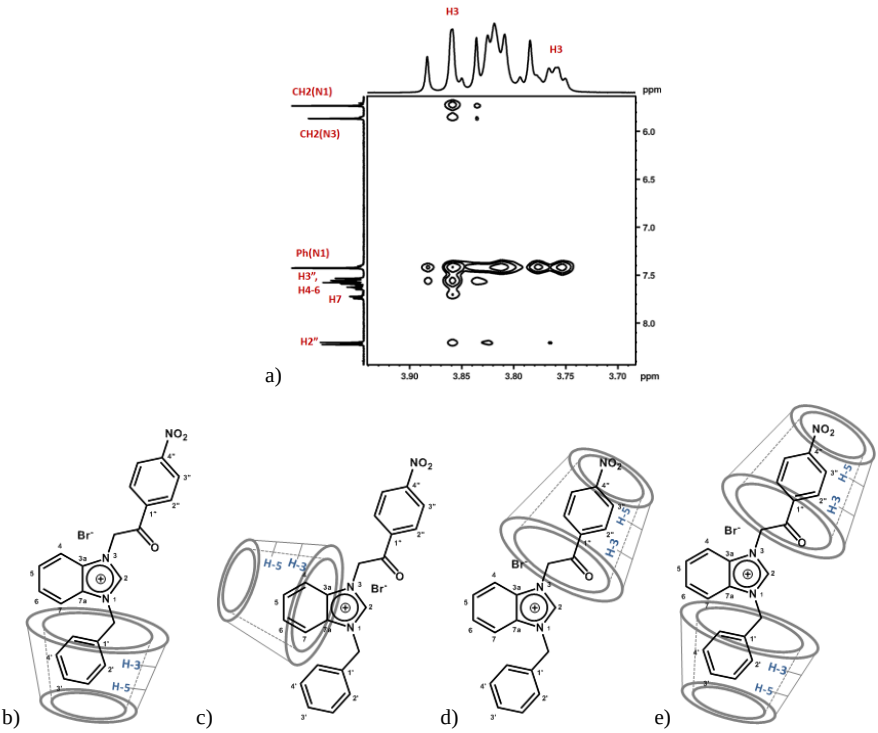


Figure 7. a) Detail of ROESY spectrum for **Bz1255-BCD** evidencing the couplings between Bz1255 and H3 and H5 from **BCD** and schematic representation of possible inclusion geometries: b) with phenyl from N1 inside the cavity, c) with the benzimidazolium residue partially inside the cavity; d) with p-nitrophenyl inside the cavity; e) 1:2 type structure, with both substituents in 2 different cavities.

The stoichiometry of the complex was determined by continuous variation method as being 1:2. The effect of some factors on complexation (temperature, pH, internal standard TSP and presence of DMSO-d_6 as cosolvent) was studied. The complex dissociates with the increase of temperature but after cooling the equilibrium is restored and in the ROESY spectrum all the couplings are seen as before heating. The complex is stable in a large pH interval. The ROESY spectrum shows couplings between the salt and the cyclodextrin at pH=2.5 and at pH=10. In the presence of internal standard TSP the complex is dissociated and complexation occurs exclusively between cyclodextrin and TSP. This is evidenced in the ROESY experiments by the disappearance of correlation peaks between the salt and cyclodextrin and the appearance of correlation peaks between TSP and cyclodextrin. Dissociation of the complex also occurs when DMSO-d_6 is present in solution.

Another study was performed on the complexation between BzB122 and β-cyclodextrin and some modified cyclodextrins. In the 1H-NMR spectra, chemical shift differences are observed when comparing the spectra for the free components with the one for the complex.

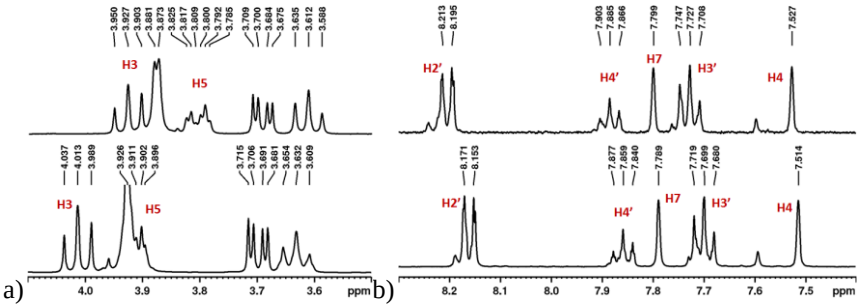


Figure 8. a) Detail of the cyclodextrin peaks region of 10 mM BCD (down) compared to 1,25 mM BCD/8,75 mM BzB122 (up) and b) detail of the salt peaks region for 10 mM BzB122 (down) compared to 1,25 mM BzB122/8,75 mM BCD (up).

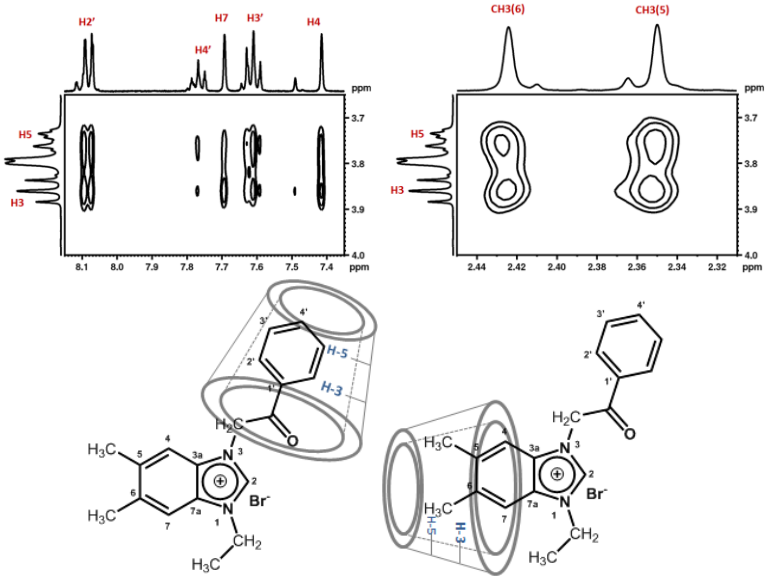


Figure 9. Details of the ROESY spectrum for **BzB122-BCD** in D_2O and schematic representations of possible inclusion geometries

The stoichiometry of this complex is 1:1 as determined by continuous variation method using NMR and UV data.

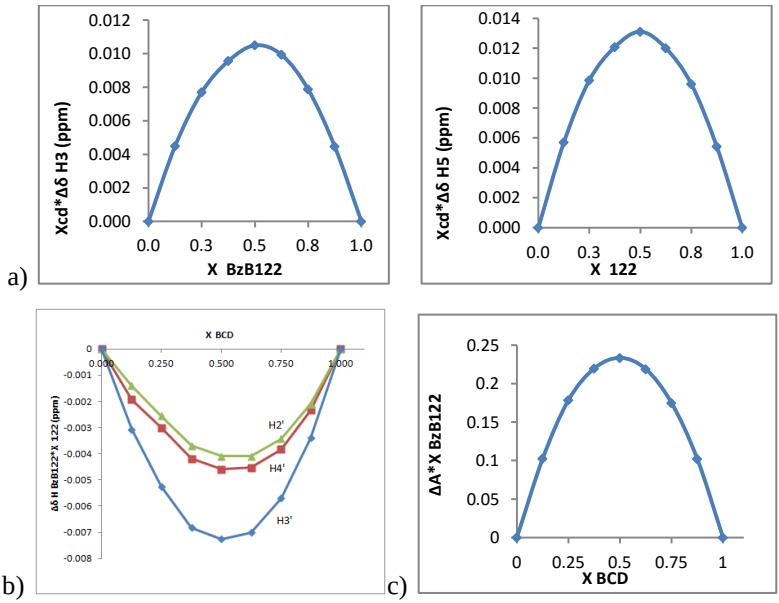


Figure 10. Job's plots of $X_{cd}*\Delta\delta_{Hcd}=f(X_{BzB122})$ for chemical shifts of H3 and H5 from BCD (a) $X_{BzB122}*\Delta\delta_{HBzB122}=f(X_{BCD})$ for chemical shifts of H3', H4' and H2' from BzB122 (b), and (c) $X_{BzB122}*\Delta A_{BzB122}=f(X_{BCD})$ for the absorbance (A) of BzB122

For this complex the association constant was determined by NMR. Data were processed with the Benesi-Hildebrand method and with 2 more elaborated computer programs, Consteq and WinEqNMR. The complexes between BzB122 and modified cyclodextrins also have 1:1 stoichiometry. The association constants for the complexes between BzB122 and 2-hydroxypropyl-β-cyclodextrin, methyl- β-cyclodextrin and sulphobutyl ether-β-cyclodextrin were also determined.

Conclusions for chapter 5

- Five benzimidazolium derivatives were completely characterized by NMR spectroscopy using 1D and 2D experiments.

- The first study regarding some benzimidazolium salts and cyclodextrins was conducted.

- The association constants and the stoichiometries of the complexes were determined.

- The competition of DMSO-d6 with benzimidazolium salts for complexation with cyclodextrins was proven.

- The competition of internal standard TSP with benzimidazolium salts for complexation with cyclodextrins and thus the necessity of using external standards for these studies was proven.

- It was shown that the strength of the interactions between the benzmidazolium salts and α- and β-cyclodextrins depends on the nature of the p-phenyl substituent and increases in the order F<Cl<Br. The cavity of β-cyclodextrin can accommodate substituents fron N1 and N3 while the cavity of α-cyclodextrin can accommodate only the substituent from N3.

General conclusions

- Three native cyclodextrins (α-, β- and γ-cyclodextrins), 4 cyclodextrin related sugars (glucose, fructose, sucrose, galactose), and 10 chemically modified cyclodextrins (sulfobutyl ether-β-cyclodextrin, sodium salt, monochlorotriazynyl-β-cyclodextrin, sodium salt, methyl-β-cyclodextrin, 2-hydroxypropyl-β-cyclodextrin and α-, β- and γ-cyclodextrins substituted with oligolactate residues) were completely characterized by NMR spectroscopy.

- The four sugars were quantified in complex aqueous matrices (fruit juices) and a statistic PCA model was developed for chemometric separation of the samples.

- In the case of oligolactide substituted cyclodextrins the binding site was determined to be at position 6 of the glucopyranose units.

- The effect of temperature, pH and internal and external standards on the NMR spectra of cyclodextrins were also studied.

- In the case of the interactions between 2-chlorophenol, 4-chlorophenol and 2,4-dichlorophenol with β-cyclodextrin, the peak for H5 from inside the cyclodextrin cavity is shifted more than the peak for H3. 2,4-dichlorophenol induces the biggest shifts, then 4-chlorophenol and 2-chlorophenol induces the smallest shifts.

- The stoichiometry of the complexes between the three halogenophenols and β-cyclodextrin is 1:1 as determined by continuous variation method.

- The stability of the complexes varies in the order: ,4-dichlorophenol>4-chlorophenol>2-chlorophenol.

- The affinity of 2,7-dibromoflouren and of its polymer is greater for cyclodextrins than for cucurbit[7]uryl.

- Five benzimidazolium derivatives were completely characterized by NMR spectroscopy using 1D and 2D experiments.

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The results described in the Original Research section were partially published in 4 ISI articles and presented at scientific manifestations in 6 oral communications and 5 posters.

Dissemination of the results

Articles

1. **M. Balan**, A. Nicolescu, C. Stavarache, M. Ciobanu, C. Deleanu, "Fast NMR juice identification based on sugars and other plant metabolites from fruits", Rev. Roum. Chim., 2013, 58, 175-182

2. A. Nicolescu, **M. Balan**, E. Georgescu, F. Georgescu, L. Ursu, B. Simionescu, P. Flip, C. Deleanu, "Benzimidazolium-cyclodextrin Inclusion Complexes", Rev. Chim. (Bucharest), 2013, 64 (4), 451-455

3. A. Farcas, K. Assaf, A. M. Resmerita, S. Cantin, **M. Balan**, P.-H. Aubert, W. Nau, "Cucurbit[7]uril-based fluorene polyrotaxanes", Eur. Polymer J., 2016, 83, 256-264

4. C. Peptu, **M. Balan-Porcarasu**, A. Šišková, Ľ. Škultéty, J. Mosnáček, "Cyclodextrins tethered with oligolactides – green synthesis and structural assessment", Beilstein J. Org. Chem., 2017, 13, 779-792

Communications

1. **M. Balan**, A. Nicolescu, B. C. Simionescu, C. Deleanu, „NMR characterization of cyclodextrins in various media", *Communication*, 16th Romanian International Conference on Chemistry and Chemical Engineering, 9–12 September, **2009**, Sinaia, Romania.

2. **M. Balan**, A. Nicolescu, B. C. Simionescu, C. Deleanu, „Influence of experimental factors on the NMR spectra of cyclodextrins", *Communication*, The Days of the Iasi Academy, 8-10 Octomber **2009**, Iasi, Romania.

3. **M. Balan**, A. Nicolescu, B. C. Simionescu, C. Deleanu, "Influence of temperature and solvents on the NMR spectra of cyclodextrins", *Communication*, The XXXI-st Romanian Chemistry Conference, 6-8 Octomber **2010**, Ramnicu-Valcea, Romania, Abstract book ISBN 978-973-750-194-3, p 29.

4. M. Ciobanu, **M. Balan**, C. Stavarache, A. Nicolescu, „Discriminarea rapida a sucurilor de fructe prin analiza statistica a spectrelor 1H-RMN", *Communication*, The Days of the Iasi Academy, Iasi, 3-5 Octomber **2013**, Abstract book p. 76.

5. **M. Balan**, A. Nicolescu, C. Deleanu, B. C. Simionescu, "Caracterizarea RMN a unor complecsi de incluziune ai ciclodextrinelor", *Communication*, The Days of the Iasi Academy, Iasi, 24-26 Septembrie **2015**, Abstract book p. 59.

6. **M. Balan-Porcarasu**, A. Nicolescu, E. Georgescu, F. Georgescu, B. C. Simionescu, C. Deleanu, "NMR Characterization of imidazolium-cyclodextrine inclusion complexes", *Communication*, The 3rd International Conference on Analitical Chemistry, 28-31 August **2016**, Iasi, Abstract book p. 42.

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1. A. Danila, M. Deleanu, A. Iorgu, C. Moise, **M. Balan**, C. Stavarache, A. Nicolescu, "NMR discrimination of fruits based on plant metabolites present in natural plant metabolites present in natural or industrial processed mixtures", *Poster*, The XXXII-nd Romanian Chemistry Conference, Calimanesti-Caciulata, 03-05 Octombrie **2012**, Abstract book p. 30.

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3. A. Nicolescu, **M. Balan**, C. Stavarache, E. Georgescu, F. Georgescu, B. C. Simionescu, P. Filip, C. Deleanu, „Benzimidazolium-Cyclodextrin Inclusion Complexes", *Poster*, The XXXIII-rd Romanian Chemistry Conference, 1-3 Octombrie **2014**, Calimaneati-Caciulata, Valcea, Romania, Abstract book p. 15.

4. **M. Balan**, C. Stavarache, E. Georgescu, F. Georgescu, A. Nicolescu, C. Deleanu, "Inclusion Complexes of Natural Cyclic Oligosaccharides", International Workshop "Food Chemistry & Engineering" 15 May **2015**, Abstract book p. 27.

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