We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

4,800
Open access books available

122,000
International authors and editors

135M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

CLARIVATE ANALYTICS BOOK CITATION INDEX INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Chapter 19

Cyclodextrin Based Spectral Changes

Lida Khalafi and Mohammad Rafiee

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/52824

1. Introduction

1.1. Cyclodextrins

A cyclodextrin (CyD) is a cyclic oligomer of α-D-glucose formed by the action of certain enzymes, Bacillus amylobacter, on starch. The first reported reference to a cyclodextrin was published by Villiers in 1891 [1]. Three cyclodextrins are readily available: α-CyD, β-CyD and γ-CyD having six, seven and eight glucose units respectively. They are commonly referred to as the native CyDs. For a long time, only the three parent CyDs were known, but during the past decade many covalently modified CyDs have been prepared from the native forms [2].

The glucose units are connected through glycosidic α-1,4 bonds. As a consequence of the $^4C_1$ conformation of the glucopyranose units, all secondary hydroxyl groups are situated on one of the two edges of the ring, whereas all the primary ones are placed on the other edge. The ring, in reality, is a conical cylinder, which is frequently characterized as a doughnut or wreath-shaped truncated cone. It is, of course, the possession of this cavity that makes the CyDs attractive subjects for study. The most notable feature of cyclodextrins is their ability to form inclusion complexes (host–guest complexes) with a very wide range of solid, liquid and gaseous compounds. Complex formation is a dimensional fit between host cavity and guest molecule [3]. This phenomenon bears the name molecular recognition [4].

1.2. Inclusion complex formation

The lipophilic cavity of cyclodextrin molecules provides a microenvironment into which appropriately sized non-polar moieties can enter to form inclusion complexes [5]. No covalent bonds are broken or formed during formation of the inclusion complex [6]. The first driving force of complex formation is release of enthalpy-rich water molecules from the cavity. The second critical factor is the thermodynamic interactions between the different components of

the system (cyclodextrin, guest, solvent). The cavity size of the toroidally shaped CyDs and the structural confrmation and size of the guest molecule are the other parameters that mostly affect the formation of a guest-CyD complex [2]. As the results of this inclusion, changes of the chemical or physical properties of both host and guest molecules are generally observed; opening a wide field of applications in many areas and allowing one to monitor the process by several experimental techniques [2,7-9].

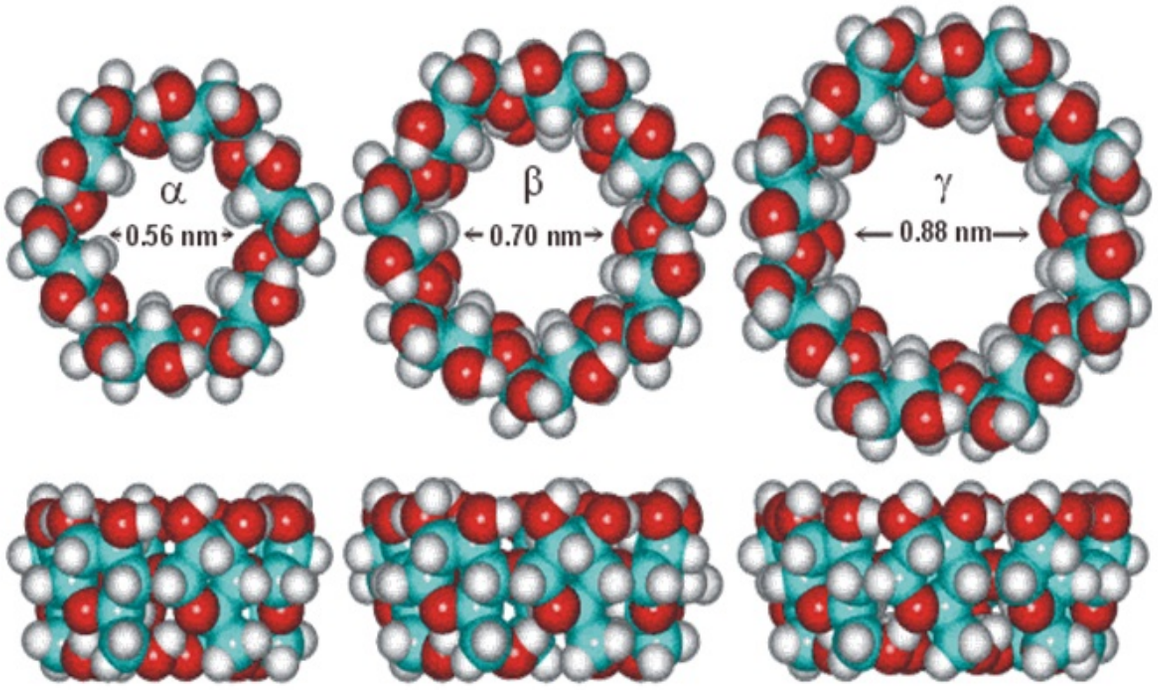

Figure 1. Structure of α-CyD, β-CyD and γ-CyD

2. Results

2.1. Cyclodextrin based spectral changes

As the result of inclusion complexes formation, the guest molecule is surrounded by the hydrophobic microenvironment of the CyD cavity. This environmental changes cause to some considerable changes in chemical properties of guest molecule such as equilibria and kinetic parameters and some changes in physical properties such as absorption coefficient or quantum yield, these changes strongly depend on the difference between CyD cavity and the outer medium.

Spectroscopic techniques are the most frequent ones which have been used for the study of these changes. Although it should be noted that the phase-solubility is one of the simplest techniques which have been used other than spectroscopy [10].

http://dx.doi.org/10.5772/52824

Some of the spectroscopic techniques such as UV-Visible, fluorescence, and NMR spectroscopy are compatible for the spectral study of the complexes that obtained in solution [11]. But the infrared spectroscopy, X-ray diffraction, scanning electron microscopy techniques [12,13] and differential scanning calorimetry [14], are suitable for the inclusion compounds that obtained in the solid state.

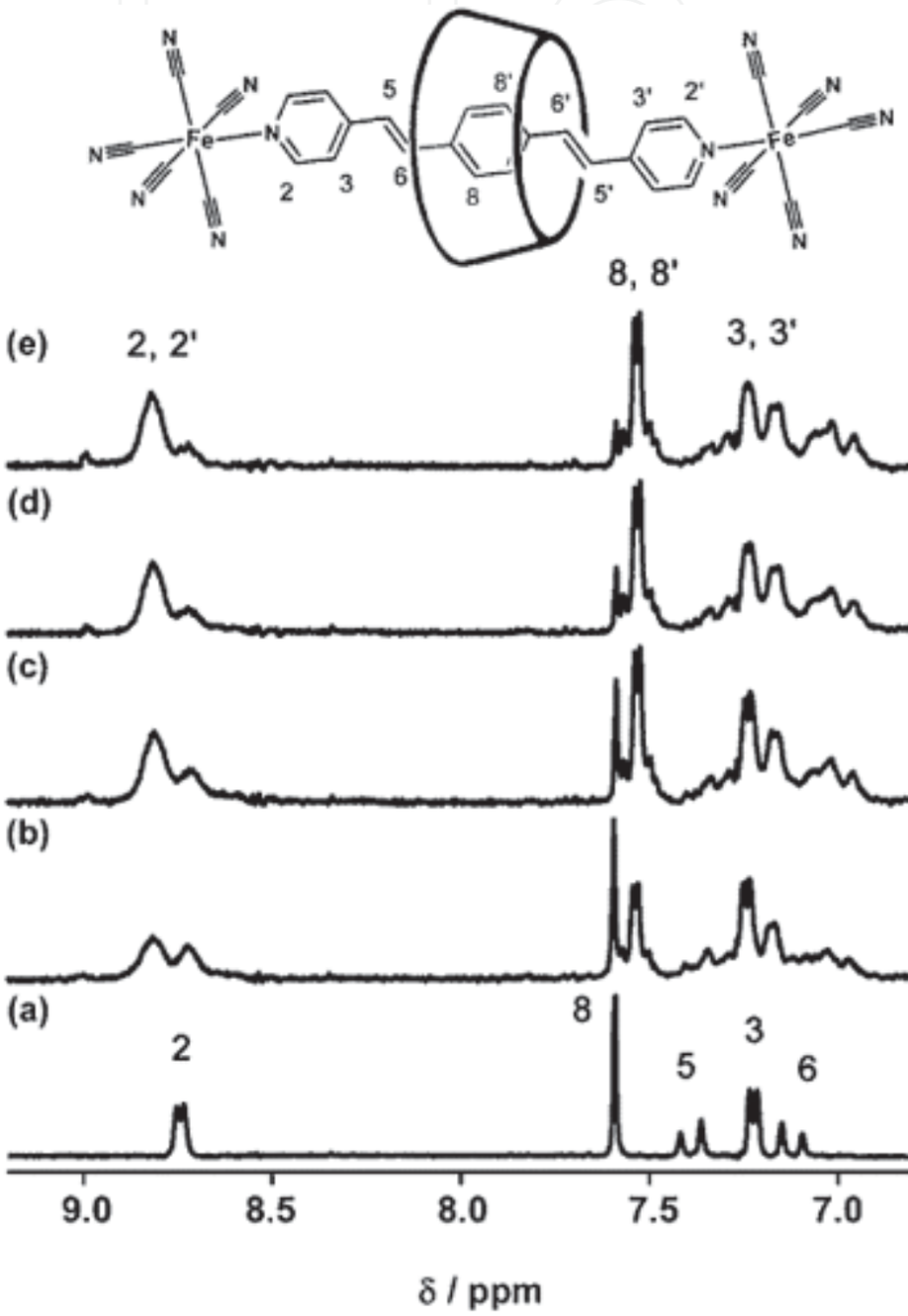

Figure 2. NMR spectra of the trans-1,4-bis[(4-pyridyl)ethenyl]benzene (BPEB) bridged ligand as function of time for the self-assembling $\{[Fe(CN_5)]_2(BPEB.\beta\text{-}CyD)\}^{6-}$ rotaxane, upon addition of 2 equivalents of β-CyD to the dimer in D_2O: (a) 0 min, (b) 5 min, (c) 30 min, (d) 60 min and (e) 24 hours.

Among the above techniques some of them such as X-ray diffraction and NMR are proper for obtaining qualitative information about the inclusion complex. For example ^{1}H NMR spectra can give us some information about the host to guest mole ratios and stability constant and even the orientation of the guest in the host cavity in solution which no other technique can give.

This section provides a condensed overview of the quantitative applications of host-guest interactions and molecular recognition which are well-matched with more quantitative techniques such as UV-Vis absorption and fluorescence.

2.2. UV. Vis. Spectral changes

In spite of the small effects encountered in absorption, peak shifts of the order of a few nm and changes of the absorption coefficients less than ten percent, UV-Vis spectrometry is an easily performed first test of the occurrence of complexation in particular in nonfluorescing systems. Moreover, the power of modern chemometric techniques allows valuable analytical applications of small effects of CyD inclusion on UV-Vis spectra. The emphasis of absorption changes and absorption studies will be on the apparent changes in the chemical properties of guest molecules, such as acid–base equilibrium. The most distinguished work in this field is report by Taguchi [15]. He has demonstrated that upon the binding of phenolphthalein to β-CyD cavity in aqueous solution at pH 10.5, the red-colored dianion form is rapidly transformed into a colorless lactonoid form.

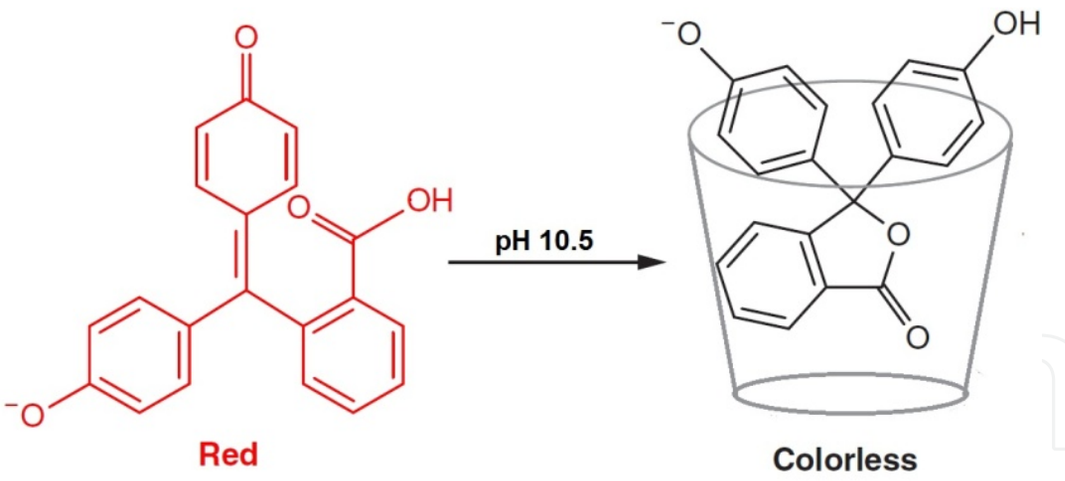

Figure 3. Proposed mechanism for the colour change of phenolphetalein in the presence of β-CyD.

This effect and some other similar spectral changes may reflect the altered polarity of the cavity microenvironment and preferential or specific guest–host interactions and stabilization of the preferred form and suppression of the other form in equilibrium. This is not a comprehensive review but is mainly intended to provide illustrative examples.

The absorption spectrum of mycophenolate mofetil (MMF) at mild acidic solutions shows an absorption band which has an absorption maximum at 302 nm for its acidic form (HMF). With

the increasing of pH, the absorption at 302 nm gradually decreased whereas the absorption with the 340 nm maximum, for the basic (MF^-) form, increased, Fig.4. These spectral changes and presence of an isobestic point indicate the presence of acid base equilibrium for this immunosuppressant drug.

The spectra of MMF in the presence of varying amounts of β-CyD at constant pH that both acidic and basic forms are presented in solution are shown in Fig. 5. The spectral change by increasing the β-CyD concentrations at constant pH is similar to the decreasing the pH of aqueous MMF solution. These spectral changes indicate suppression of the basic form and dominance of acidic form in the presence of β-CyD cavity.

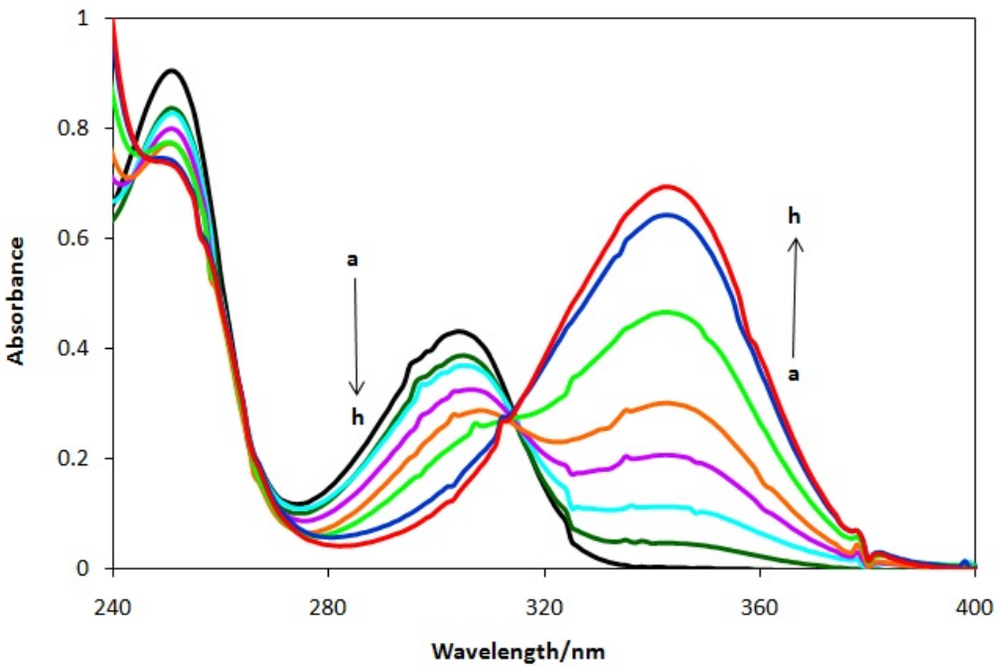

Figure 4. The absorption spectra for 4.0×10^{-4} mol L^{-1}MMF at various pH values. The pH values are (a) 5.0, (b) 6.5, (c) 7.0, (d) 7.5, (e) 8.0, (f) 8.5, (g) 9.0 and (h) 9.5. [Reprinted from Khalafi L, Rafiee M, Mahdiun F, Sedaghat S. / Spectrochim. Acta Part A., 2012; 90 45-49 with permission from Elsevier Science.]

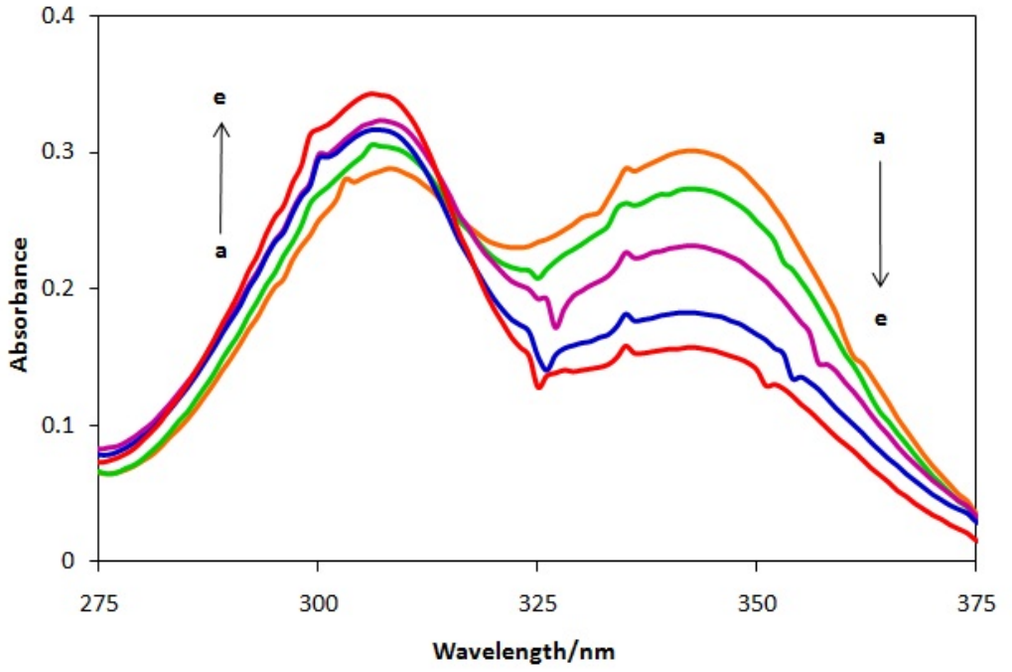

Figure 5. The absorption spectra for 4.0×10^{-4} mol L^{-1}MMF in the presence of different concentrations of β-CyD at pH 8.0. The concentrations of β-CyD are: (a) 0.0, (b) 1.0×10^{-3}, (c) 2.0×10^{-3}, (d) $4.0\times10^{-3}$and (e) 8.0×10^{-3} M. [Reprinted from Khalafi L, Rafiee M, Mahdiun F, Sedaghat S. / Spectrochim. Acta Part A., 2012; 90 45-49 with permission from Elsevier Science.]

Rank Annihilation Factor Analysis (RAFA) is used as an efficient chemometrics algorithm for the analysis of spectrophotometric data and the conditional acidity constant of MMF and the stability constant of its acidic and basic forms were obtained in the absence and presence of β-CyD. Based on these results with increasing β-CyD concentration the acidic form stabilized and the equilibrium of the system driving to produce acidic form. Consequently the conditional acidity constant decrease with increasing the β-CyD concentration [16]. The spectrophotometric study of neutral red and 4-nitrophenol in the presence of β-CyD are the other examples of spectral changes with different preferential complexation.

In the case of neutral red the increase in the acidity constants as a function of β-CyD is indicative of more stabilization of basic (neutral) form rather than positively charged acidic form. Whereas the study of acid-base equilibrium of 4-nitrophenol show that 4-nitrophenolate (the negatively charged basic form) has more affinity than the acidic (neutral) form. It has been claimed that the driving force of more stable inclusion complex of 4-nitrophenolate with β-CyD is the hydrogen bonding [17, 18].

The above results and some other comprehensive studies show the effect of interaction of guest molecules with microenvironment of β-CyD cavity. The CyD nanocavity has the characters similar to an 80% dioxane/water solution and provides a slightly alkaline environment [19]. There are four possible interactions including; hydrophobic, hydrogen binding, Van der Waals forces and donor-acceptor for the cavity that affect the favored interaction, equilibrium shift and spectral changes in the presence of β-CyD [20-22].

2.3. UV. Vis. based Molecular recognition:

The spectral change of an indicator may not be important in molecular recognition itself, but there is an important concept named as "indicator displacement assay" and/or "spectral displacement" which have been developed considering theses spectral changes. Spectral displacement method involves the color changes upon addition of competitive guest molecules; the dye moiety was excluded from the CyD cavity and located in the aqueous media. In that state, by environmental changes around the dye moiety, the dye moiety shows its normal color changes resulting from pH changes [23].

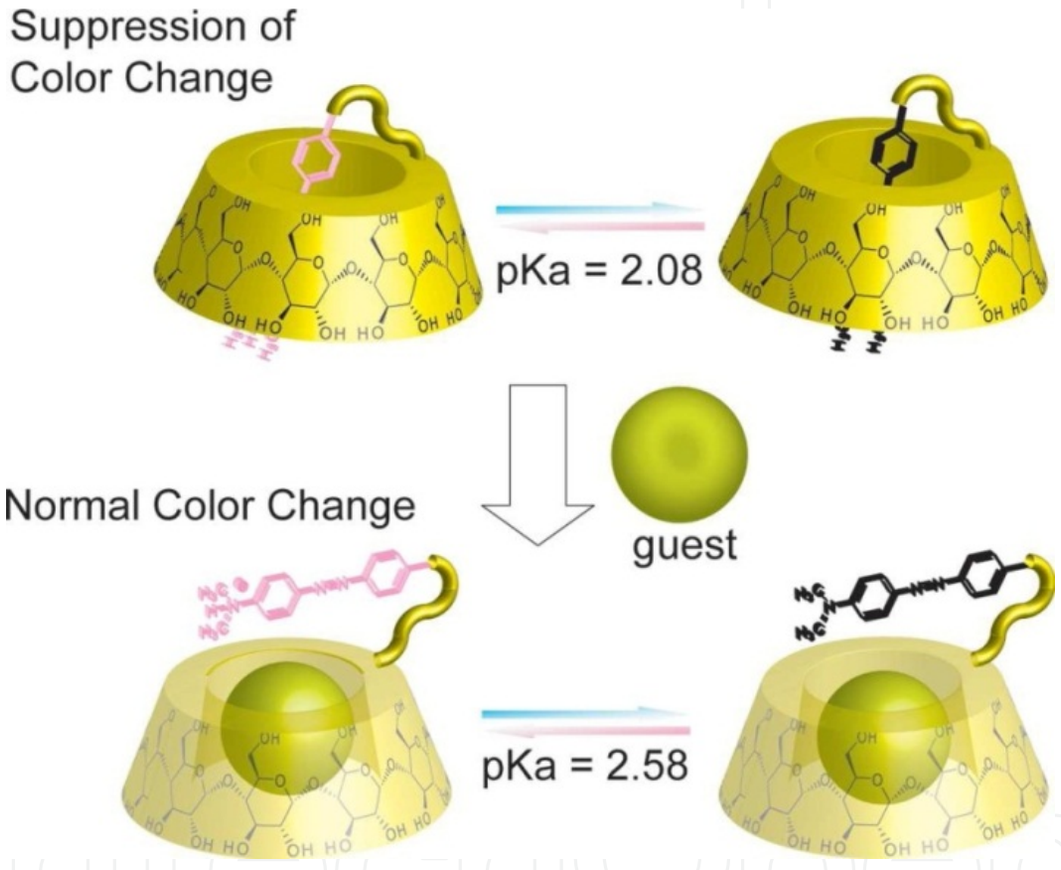

Figure 6. *p*-Methyl red appended β-CyD chemical sensor

A spectroscopic displacement method is used to determine association constants or the concentrations of the compounds that are spectroscopically transparent. Each application may be divided into two classes, the first one is based on competitive inclusion of guest and indicator in the solution, and the second one is the competition of dissolved guest with the CyD bonded indicators.

The success of the visible spectral displacement technique involving methyl red, in bonded form, as the competing reagent applied for the construction of molecular sensor for adamanetanccarboxylic acid, adamantanol, borneol, cyclaxtanol, cyclohexanol and same structures [24, 25].

The spectrophotometric technique involving phenolphthalein as the competing reagent appears to be the most promising one. It is based on the fact that in alkaline solutions a colourless 1:1 complex is formed between phenolphthalein and β-CyD that the red phenolphthalein dianion is partially displaced by a competing reagent to an extent depending upon its affinity to form a complex with the CyD host. Phenolphthalein-modified β-CyD was synthesized for the purpose of developing a new type of guest-responsive color change indicator and the guest-induced absorption changes were used for molecule sensing [26, 27].

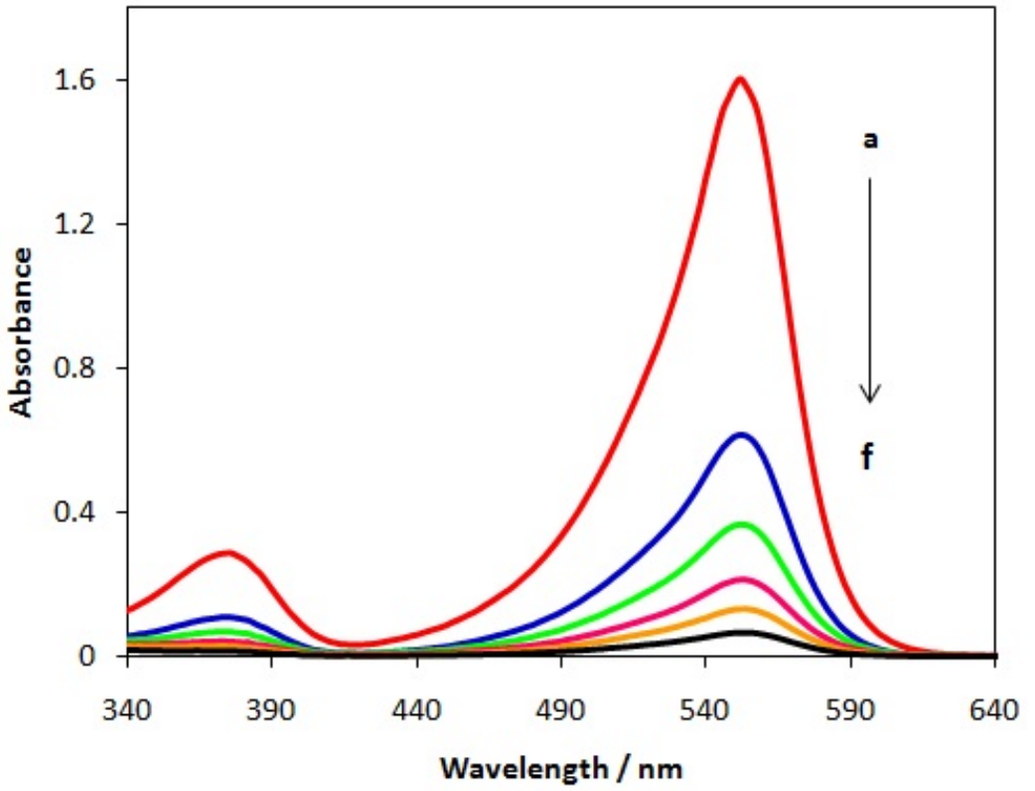

Figure 7. Absorption spectra for 4.8×10^{-5} mol L^{-1} phenolphthalein in the presence (a) 0.0, (b) 1.0×10^{-4}, (c) 2×10^{-4}, (d) 4×10^{-4}, (e) 7×10^{-4}, and (f) 1.0×10^{-3} mol L^{-1} of β -CyD at pH 10.5. [Reprinted from Afkhami A, Madrakian T, Khalafi L. / Anal. Lett, 2007; 40 2317-2328 with permission from Taylor & Francis.]

Several attempts have been also made on color changes based on competitive complexation of some important chemicals with phenolphthalein-CyD inclusion complex. These chemical sensors are relatively inexpensive, rapid and simple for determination of desired compounds, such as pharmaceuticals, surfactants and fatty acids which are transparent in the visible range [28-34]. The sensing abilities of for various guests are roughly parallel to the binding constants. Fig. 8 shows that by addition of ibuprofen to the phenolphthalein-β-CyD complex solution, the absorbance at 554 nm increases. This increase in the absorbance is due to the decomposition of phenolphthalein- β-CyD inclusion complex by displacement of ibuprofen by phenolphthalein. This phenomenon indicates competition of the ibuprofen with phenolphthalein in the formation of inclusion complex

with β-CyD. The amount of increase in the absorbance at 554 nm was found to be proportional with the ibuprofen concentration over a certain concentration range.

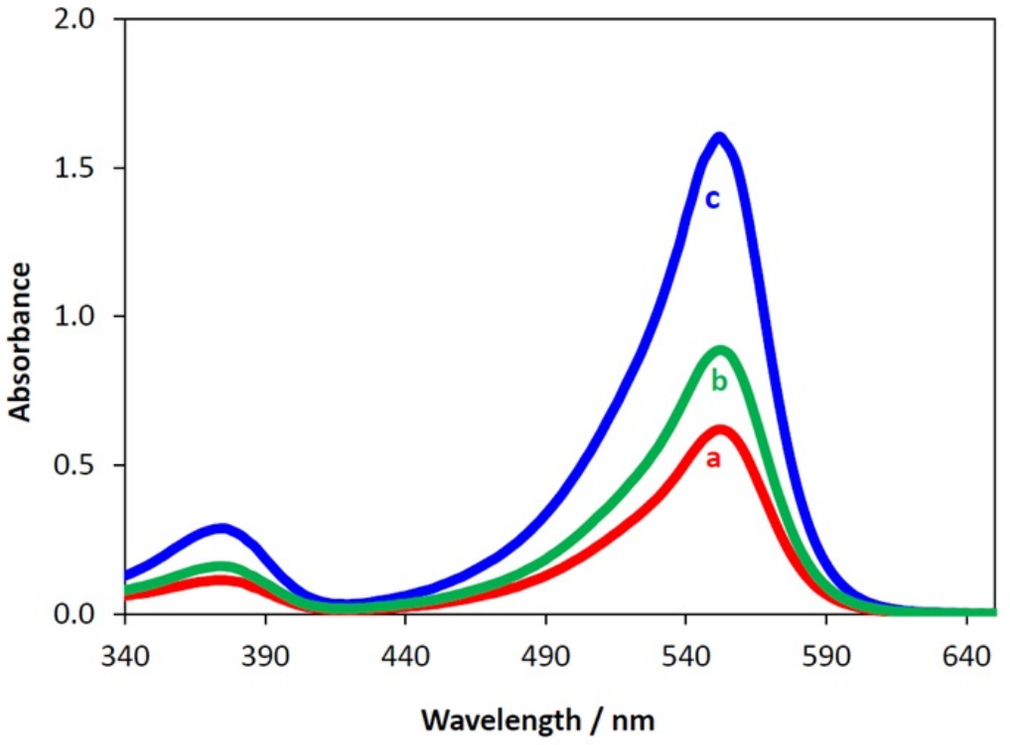

Figure 8. Absorption spectra for 4.8 ×10^{-5} mol L^{-1} phenolphthalein at pH 10.5 in the presence of (a) 1.0×10^{-4} mol L^{-1} β-CyD and 2.0×10^{-4} mol L^{-1}ibuprofen, (b) 1.0×10^{-4} mol L^{-1} β-CyD and (c) in the absence of β-CyD and ibuprofen. [Reprinted from Afkhami A, Madrakian T, Khalafi L. /Anal. Lett, 2007; 40 2317-2328 with permission from Taylor & Francis.]

Color change chemical sensors of CyD derivatives carrying dyes such as nitrophenol [35] and alizarin yellow [36] were reported that relies on direct measurements of some analytes.

Also there is an example of color and spectral change of metal ion-indicators that affected by β-CyD. Recently it has been demonstrated that the addition of β-CyD to the solution containing the complex of calcium and magnesium with Eriochrome Black T (EBT) caused decomposition of the 1:1 metal complex and increase in EBT concentration in solution due to the formation of EBT-β-CyD inclusion complex. At a given pH, the values of metal ion conditional formation constant (K'_f) decreased by increasing β-CyD concentration based due to the formation of an inclusion complex between the desired form of EBT and β-CyD. The amount of decrease in K'_f with increasing β-CyD concentration and

the color changes due to complex decomposition depends on the stability of the inclusion complex between EBT and β-CyD [37].

There is a large volume of published studies reporting the affinities and even selective affinity of secondary hydroxyl side of CyDs for metal ion binding and complexation [38]. This complexation ability improves considerably by structural and functional groups modification. The secondary hydroxyl groups are deprotonated and coordinated to bind Pb(II) ions forming a hexadecanuclear lead(II) alkoxide [39]. Two amino groups introduced on the primary hydroxyl side of β-CyD can chelate a platinum ion [40]. 6-amino-glucopyranose analogue of β-CyD had binding affinity for metal ions with Cs^{+} selectivity [41]. In 2010, Pitchumani et al. reported a per-6-amino-β-CyD as a supramolecular host and p-nitrophenol as a spectroscopic probe as a novel colorimetric and ratiometric sensor for transition metal cations, Fe^{3+} and Ru^{3+} in water. Binding of these cations causes an appreciable change in the visible region of the spectrum which can be detected by naked-eye and is insensitive to other metal ions namely Ag^{+}, Cu^{+}, Mn^{2+}, Fe^{2+}, Cu^{2+}, Zn^{2+}, Cd^{2+}, Hg^{2+}, Pb^{2+}, Cr^{3+}, La^{3+} and Eu^{3+}. The color change and consequent sensing ability is significant at equimolar ratio of host and guest and also at very low concentration [42].

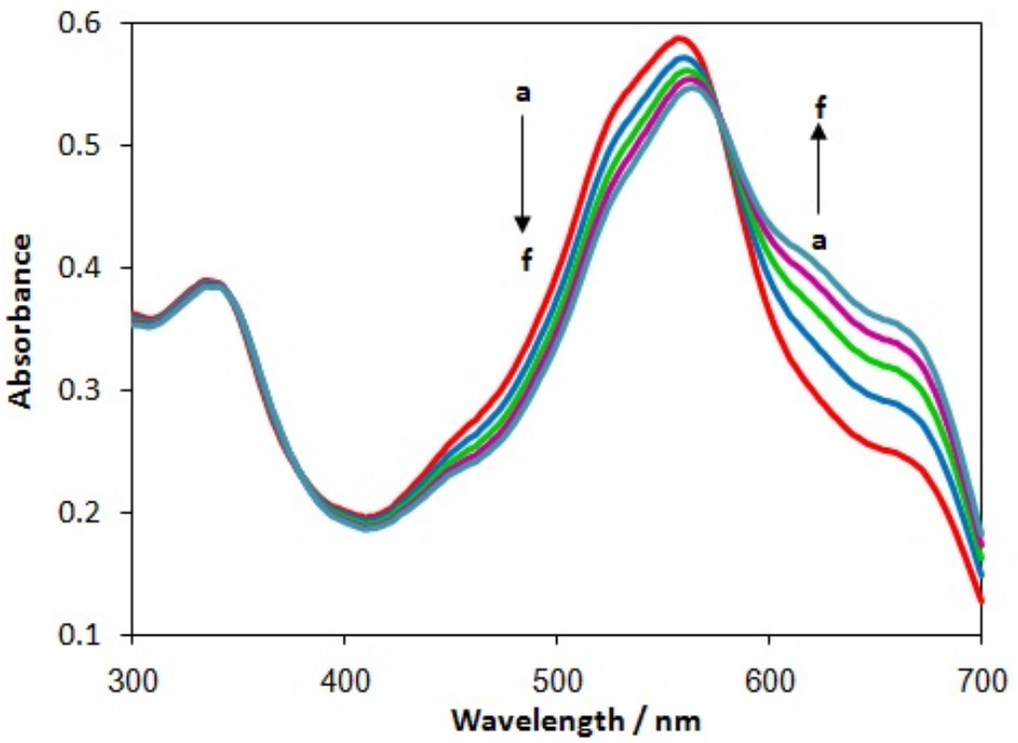

Figure 9. The spectra of Ca-EBT complex (1.0×10^{-3} mol L^{-1} Ca^{2+} and 4.0×10^{-5} mol L^{-1} EBT) in the presence of (a) 0.0, (b) 3.0×10^{-3}, (c) 6.0×10^{-3}, (d) 9.0×10^{-3}, (e) 1.2×10^{-2} and (f) 1.5×10^{-2} mol L^{-1} of β-CyD at pH 9.5. [Reprinted from Afkhami A, Khalafi L. / Supramol. Chem., 2008; 19 579-586 with permission from Taylor & Francis.]

http://dx.doi.org/10.5772/52824

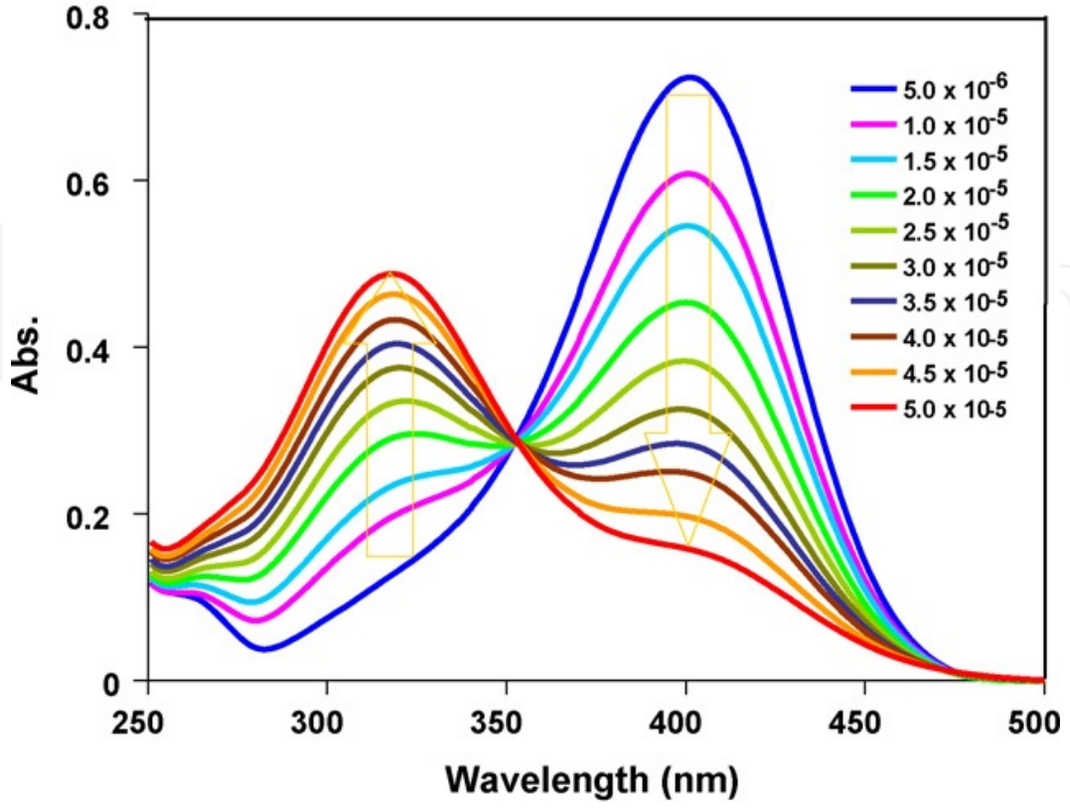

Figure 10. UV–Vis spectra of per-6-amino-β-CyD/p-nitrophenol (5×10^{-5} M) upon addition of Ru^{3+} (5×10^{-6}M to 5×10^{-5} M). [Reprinted from Suresh P. Abulkalam Azath I, Pitchumani K. / Sens. Actuators, B 2010; 146 273-277 with permission from Elsevier Science.]

Numerous studies have attempted to explain the possibility of incorporation of CyDs and modified CyDs in the structures of ternary complexes as ligand. In some of them the whole complex act as a guest and the metal ion has no direct contact with CyD [43]. In some other complexes the CyD appears as a coordinating ligand [44-49]. For example the Imidazole-appended β-CyD forms a ternary complex with a Cu^{2+} ion and l-tryptophanate [50]. The 6-amino and imidazolyl groups of the host molecule and the carboxyl and amino groups of l-tryptophanate are coordinated to the Cu^{2+} ion.

Moreover the cavity microenvironment of CyDs may alter the rate constant of reactions for the guest molecules depend on the reaction, substrate and the differences between cavity and solvent environments [51-53]. The changes in reaction rate cause to spectral time profile of the substrate and may be applicable in selective kinetic measurement of substrates and their recognition [54, 55].

2.4. Luminescence based molecular recognition

CyD inclusion is a means for protection of an excited state luminescent guest from the solvent environment that frequently shows a marked increase of luminescence due to increase in quantum yield and lifetime [56]. It have been mentioned even in some textbook that addition of CyD in solution is an efficient way in attaining the room temperature phosphorescence. This

effect is usually much larger than that observed in absorption, and has therefore been used more efficiently and sensitively for luminescencing substrates. 6-bromo-2-naphthol is a good example that exhibited room temperature in the presence of β-CyD owing to protection from O_2 quenching in a nondeoxygenated solution, although nitrogen purging increased the emission intensity 13-fold [57].

For 2-chloronaphthalene solutions containing both d-glucose and α-CyD, the room-temperature phosphorescence of 2-chloronaphthalene has been observed. The 2:1 inclusion complex is responsible for the room-temperature phosphorescence. The quantum yield of the room-temperature phosphorescence from the 2:1 inclusion complex has been determined to be 19% of alcoholic solution at 77 K. When KI is added an enhancement is observed in phosphorescence intensity due to the formation of a ternary inclusion complex with iodide. Also the intensity reduction at higher concentrations of KI seems to be due to the formation of a nonphosphorescent ternary inclusion complex containing two iodides [58]. The notion of "turn-on" fluorescent sensor is used for this molecular recognition mechanism.

For the crown ether fluoroionophore/ β-CyD complex, the dimerization of the fluoroionophore inside the β-CyD is found to be selectively promoted by alkali metal ion binding, thereby resulting in metal-ion-selective pyrene dimer emission in water. This supramolecular function is successfully utilized in the design of a podand fluoroionophore/β-CyD complex for sensing toxic lead ion in water [59, 60].

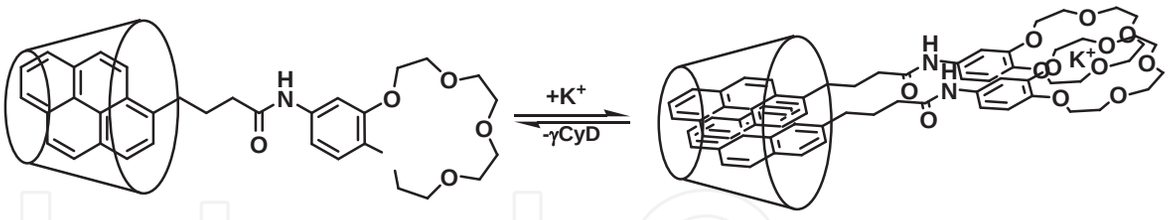

Figure 11. Response mechanism of benzo-15-crown-5 fluoroionophore /γ-CyD complex for K^+ in water.

A further interesting application of fluorescence spectroscopy is its potential enantioselectivity. Chiral discrimination has been demonstrated for CyD inclusion of camphorquinone [61]. The measurement of fluorescence anisotropy has been proposed as a method to determine the enantiomeric composition of samples [62].

As well as UV-Visible spectroscopy; competition of desired analyte with CyD-bonded or dissolved fluorophore yields a significant change in the fluorescence signal that will be useful in molecular recognition. Various "turn-off" fluorescent chemical sensors, in which fluorescence intensity was decreased by complexation with guest molecules, were reported.

http://dx.doi.org/10.5772/52824

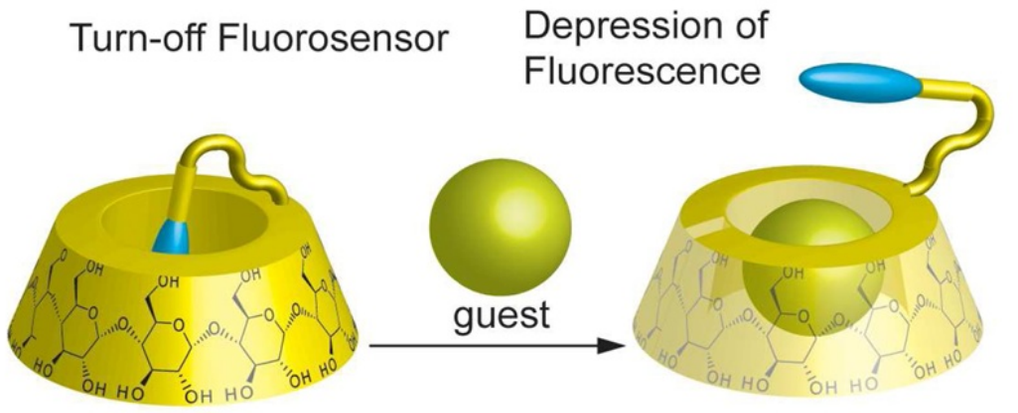

Figure 12. The mechanism of action for a turn-off fluorosensors.

A comprehensive example molecular recognition based on both decrease and increase in fluorescence intensity is the dansyl bonded CyD with diethylenetriamine spacer (CyD-dien-DNS) which have been reported by Corradini et al. In the presence of lipophilic organic molecules, CyD-dien-DNS showed sensing properties due to competitive inclusion of the guest and "in-out" movement of the dansyl group. CyD-dien-DNS was found also to be a fluorescent chemosensor for copper(II) ion, with a linear response and good selectivity, suggesting that a more flexible conformation of the linker and the presence of additional binding sites allow binding of the metal ion by the amino and sulfonamidate groups.

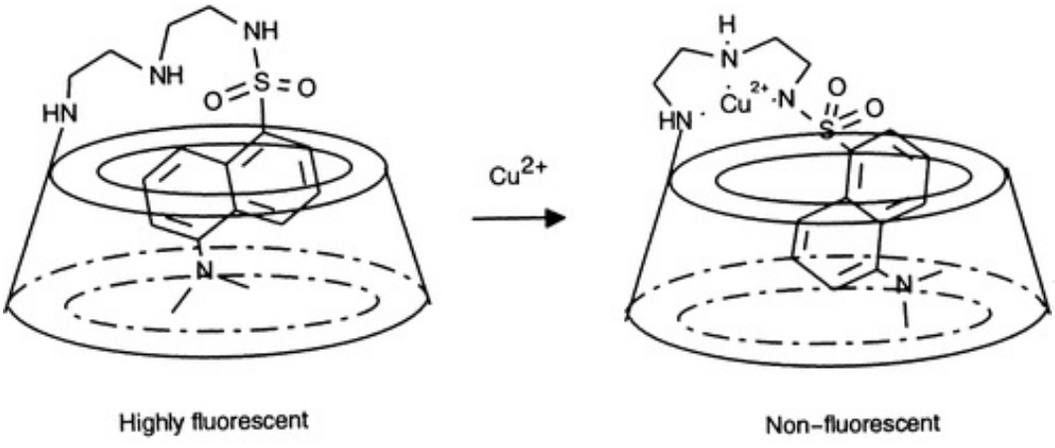

Figure 13. Spectral change of dansyldiethylenetriamine modified cyclodextrin in the presence of copper ion. [Reprinted with permission from Corradini R, Dossena A, Galaverna G, Marchelli R, Panagia A, Sartor G. / J. Org. Chem., 62, 6283 (1997). Copyright 1997, American Chemical Society.]

The CyD-dien-DNS copper(II) complex was shown to behave as a chemosensor for bifunctional molecules, such as amino acids. In fact, upon addition of alanine, tryptophan, and thyroxine, the negligible fluorescence intensity of Cu(CyD-dien-DNS) complex was "switched on", with a response dependent on the amino acid side chain [63]. Fluorescent indolizine

modified CyD were studied in aqueous solution to evaluate their potentialities as molecular chemosensors for volatile organic compounds (VOCs) such as adamantanol, benzene, toluene, phenol and p-cresol as guest. The formation constant values measured using a spectral displacement method and also some specific algorithm treatments are reported for their quantitative analysis. [64, 65]. Some phenylseleno derivatives of CyD have been synthesized as chiral molecular sensors. These modified cyclodextrins can recognize both the size and chirality of the guest molecules despite of this fact that their stability constants with aliphatic alcohols are generally smaller than those for native β-CyD [66].

Moreover some chiral amino acid modified CyDs have been synthesized as chiral molecular sensors. N-dansyl-L-Phe-modified β-CyD showed high D-selectivity for norbornane derivatives and N-dansyl-D-Phe-modified β-CyD showed high L-selectivity for menthol [67]. Time-resolved fluorescence studies showed that the fluorescence of the dansyl group was completely quenched in the ternary complexes formed, and that the residual fluorescence was due to uncomplexed ligand. The enantioselectivity in response was found to be due to the formation of diastereomeric ternary complexes [68,69]. Fluorophore-amino acid-CyD were synthesized and characterized as fluorescent indicators of molecular recognition [70]. A novel boronic acid fluorophore 1/β-CyD complex sensor for sugar recognition in water has been designed [71].

2.5. Recognition of toxins based on spectral changes

There are also some successful applications of CyDs based spectral changes which have been used for the recognition of biologically important toxins.

Cyanotoxins are potent toxic compounds produced by cyanobacteria during algal blooms, which threaten drinking water supplies. These compounds can poison and kill animals and humans. The host−guest interactions of CyDs with problematic cyanotoxins were investigated to demonstrate the potential application of CyDs for the removal of these toxins from drinking water or applications related to their separation or purification. The complexation of these cyanotoxins with CyDs was monitored by nuclear magnetic resonance (NMR). The observed changes in chemical shifts for specific protons and competitive binding experiments demonstrate a 1:1 inclusion complex between γ-CyD and microcystins and nodularin, and the results suggest that CyD-type substrates are useful hosts for their complexation [72].

The fluorescence properties of the aflatoxins, as the most important mycotoxins, and the effect of various CyDs on their fluorescence emission were studied. The complex formation constant (K_f) of these compounds with β-CyD was chromatographically determined, and from the results obtained, it has been concluded that K_f cannot be used alone to explain the fluorescence increase [73].

An example of determination of biological toxins is a highly sensitive and rapid strategy for characterizing aflatoxins and the cholera toxin based on capillary electrokinetic chromatography with multiphoton-excited fluorescence. The aflatoxins are a highly mutagenic multiple-ringed heterocycles produced by aspergillus fungi and cholera toxin a-subunit is the catalytic domain of the bacterial protein toxin from Vibrio cholera. The anionic carboxymethyl-β-CyD, used to chromatographically resolve the uncharged aflatoxins, enhances emission from these

compounds without contributing substantially to the background [74]. Also the determination of aflatoxin B1 (AFB1) in wheat has been accomplished by enhanced spectrofluorimetry in the presence of β-CyD. The method is based on the enhanced fluorescence of AFB1 by β-CyD in 10% (w/w) methanol–water solution. The adopted strategy combined the use of parallel factor analysis (PARAFAC) for extraction of the pure analyte signal and the standard addition method, for a determination in the presence of matrix effect caused by wheat matrix [75].

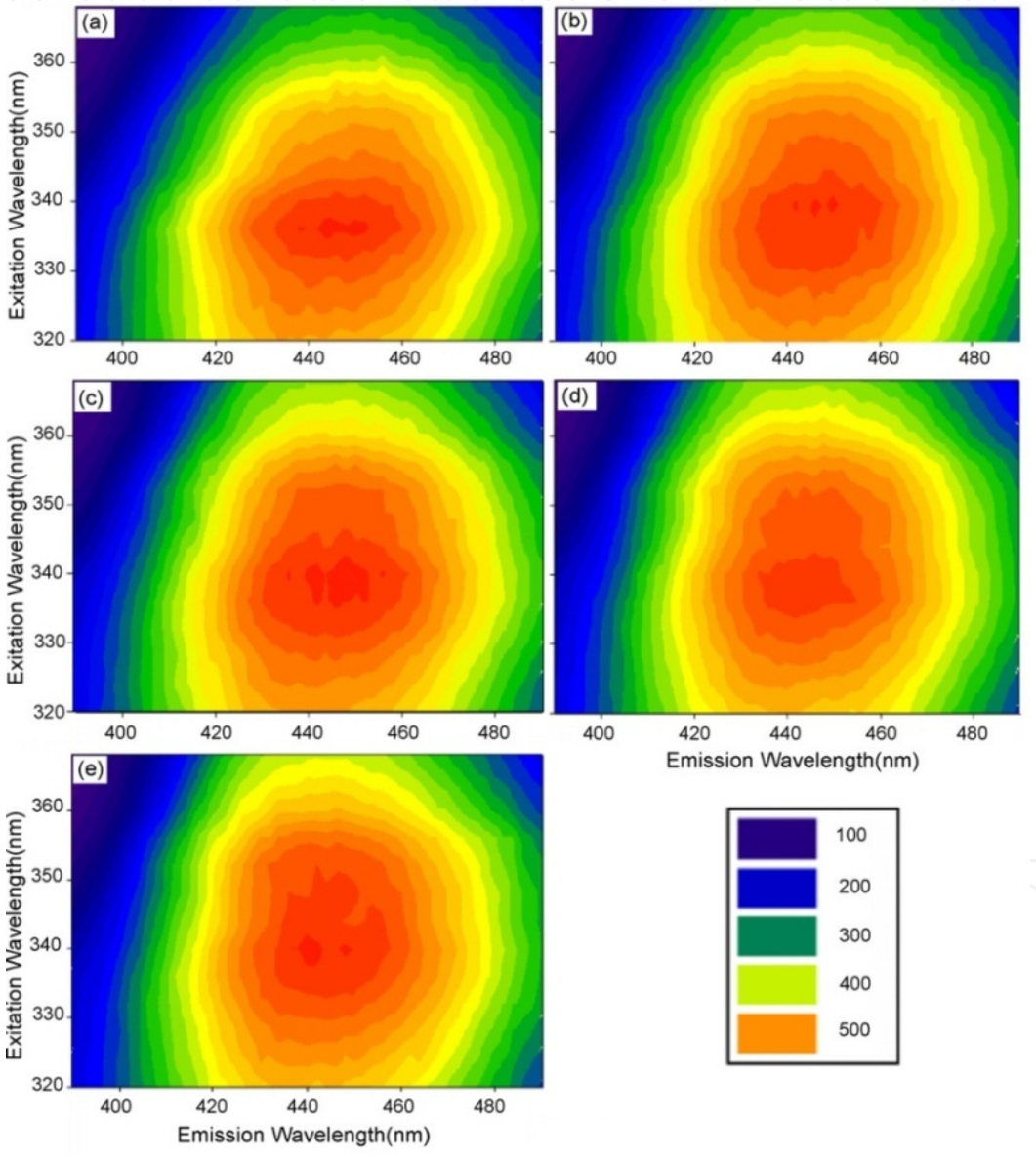

Figure 14. Contour plots (excitation–emission) for an original wheat sample and four AFB1 standard additions; (a) the original sample, (b) plus 2.0 μg kg^{-1}, (c) plus 3.8 μg kg^{-1}, (d) plus 5.7 μg kg^{-1}, (e) plus 7.4 μg kg^{-1}. [Reprinted from Hashemi J, Asadi Kram G, Alizadeh N. / Talanta, 2008; 75 1075-1081 with permission from Elsevier Science.]

2.6. Interaction and recognition of natural compounds

Finally the spectral change and interaction of some natural compounds such as alkaloids and peptides with CyDs is discussed.

Complex formation of the glutathione and some of its derivatives with bridged β-CyD such as 2,2′-diseleno-bridged β-CyD were determined by UV-Vis. absorption and ^{1}H-NMR spectroscopy [76]. Polymerization of the amyloid beta-peptide (Abeta) has been identified as a major feature of the pathogenesis of Alzheimer's disease (AD). Inhibition of the formation of these toxic polymers of Abeta has emerged as an approach for developing therapeutics for AD. NMR and circular dichroism (CD) spectra were used to investigate the interaction between CyD and Abeta. CD spectral analyses show that β-CyD inhibits the aggregation of Abeta. Analysis of the one-dimensional proton NMR spectra of the mixture of Abeta with β-CyD clearly indicates that there are chemical shift changes in the aromatic ring and the methyl groups in the peptide [77].

A series of CyDs –cinchona alkaloid inclusion complexes were prepared from β-CyD and some of its derivaties and four cinchona alkaloids, and their inclusion complexation behavior was investigated by means of fluorescence, UV/Vis and 2D NMR spectroscopy. The results showed that the cinchona alkaloids can be efficiently encapsulated in the CyD cavity in an acidic environment and sufficiently released in a neutral environment, which makes these CyD derivatives the potential carriers for cinchona alkaloids [78,79]. Using colorimetry and ^{1}H-NMR and UV spectroscopy, together with solubility methods,the interaction of natural and hydroxylpropylated CyDs with xanthine, theophylline, theobromine, and caffeine in aqueous solution have been studied [80].

Combination of the spectrophotometric methods and some separation methods such as capillary electrophoresis (CE) and micellar electrokinetic chromatography (MEKC) in the presence of CyDs have been used successfully for the quantitative analysis of natural alkaloids [80,81].

3. Conclusion

CyDs are a versatile tool in the molecular recognition and sensing. Formation of inclusion complex cause to some spectral changes which have been used successfully for the study of host-guest interactions. Additionally the desired spectral changes as the results of complex formation have been used for promote analyte detection and continue to inspire creative applications. The most sensible spectral changes were reported for chemical and fluorescence indicators. These considerable changes have been used for the study and better detection of many absorbing and especially fluorescent species. Moreover many spectrochemically silent organic and some inorganic compounds cause color/fluorescence change in CyD and indicator solutions, because of their competition to form inclusion complex. These changes cause to recognition of the target competitive hosts. On this basis some "indicator modified cyclodextrin" in which indicator is linked to cyclodextrin via a spacer, was synthesized that change color/fluorescence in response to the presence of molecules, ions and many biologically

important compounds. The guest-induced changes that are roughly parallel to its binding constants were used for molecule sensing. These are valuable for qualitative and quantitative chemical analysis. Sensitivity and selectivity improved by appropriate designing of the dye moiety or spacer.

Author details

Lida Khalafi[1] and Mohammad Rafiee[2]

1 Department of Chemistry, Shahr-e-Qods Branch, Islamic Azad University, Tehran, Iran

2 Department of Chemistry, Institute for Advanced Studies in Basic Sciences (IASBS), Zanjan, Iran

References

[1] Villiers A. Sur la fermentation de la fécule par l'action du ferment, Butyriqué Compt. Rend. Fr. Acad. Sci., 1891; 112 435-438.

[2] Szejtli J. Introduction and General Overview of Cyclodextrin Chemistry. Chem. Rev., 1998; 98 1743-1753.

[3] Szente L, Szejtli J, Kis GL. Spontaneous Opalescence of Aqueous γ-Cyclodextrin Solutions: Complex Formation or Self-Aggregation. J. Pharm. Sci., 1998; 87 778-781.

[4] Dodziuk H. Cyclodextrins and Their Complexes Chemistry, Analytical Methods, Applications. Weinheim: WILEY-VCH; 2006.

[5] Loftsson T, Brewster ME. Pharmaceutical Applications of Cyclodextrins: Drug Solubilisation and Stabilization. J. Pharm. Sci., 1996; 85 1017–1025.

[6] Schneiderman E, Stalcup AM. Cyclodextrins: A Versatile Tool in Separation Science. J. Chromatogr. B., 2000; 745 83-102.

[7] Martin Del Valle E.M. Cyclodextrins and Their Uses: A Review. Process Biochem., 2004; 39 1033-1046.

[8] Karathanos VT, Mourtzinos I, Yannakopoulou K, Andrikopoulos, NK. Study of the Solubility, Antioxidant Activity and Structure of Inclusion Complex of Vanillin with β-Cyclodextrin. Food Chem. 2007; 101 652-658.

[9] Buschmann HJ, Schollmeyer E. Applications of Cyclodextrins in Cosmetic Products: A Review. J .Cosmet. Sci. 2002; 53 185-191.

[10] Connors KA. The Stability of Cyclodextrin Complexes in Solution. Chem. Rev., 1997; 97 1325-1357.

[11] Toma SH, Toma HE. Self-Assembled Rotaxane and Pseudo-Rotaxanes based on β-Cyclodextrin Inclusion Compounds with trans-1,4-Bis[(4-pyridyl)ethenyl]benzene-pentacyanoferrate(II) Complexes. J. Braz. Chem. Soc., 2007; 18 279-283.

[12] Perez-Martınez JI, Gines JM, Morillo E, Rodrı´guez ML, Moyano JR. 2,4-Dichlorophenoxyacetic Acid/Partially Methylated-β-Cyclodextrin Inclusion Complexes. Environ. Technol. 2000; 21 209-216.

[13] Saikosin R, Limpaseni T, Pongsawasdi P. Formation of Inclusion Complexes between Cyclodextrins and Carbaryl and Characterization of the Complexes. J. Incl. Phenom. Macro. Chem. 2002; 44 191-196.

[14] Perez-Martinez JI, Arias MJ, Gines JM, Moyano JR, Morillo E, Sanchez-Soto PJ, Novak C. 2,4-D-Alpha-Cyclodextrin Complexes; Preparation and Characterization by Thermal-Analysis. J. Thermal Anal. 1998; 51 965-972.

[15] Taguchi K. Transient Binding Mode of Phenolphthalein- β-Cyclodextrin Complex: An Example of Induced Geometrical Distortion. J. Am. Chem. Soc., 1986; 108 2705-2709.

[16] Khalafi L, Rafiee M, Mahdiun F, Sedaghat S. Investigation of the Inclusion Complex of β-Cyclodextrin with Mycophenolate Mofetil. Spectrochim. Acta Part A, 2012; 90 45-49.

[17] Afkhami A, Khalafi L. Spectrophotometric Determination of Conditional Acidity Constant as a Function of β-Cyclodextrin Concentration for Some Organic Acids Using Rank Annihilation Factor Analysis. Anal. Chim. Acta. 2006; 569 267-274.

[18] Chandra Ghosh B, Deb N, Mukherjee A.K. Determination of Individual Proton Affinities of Ofloxacin from its UV-Vis Absorption, Fluorescence and Charge-Transfer Spectra: Effect of Inclusion in β-Cyclodextrin on the Proton Affinities. J. Phys. Chem. B, 2010; 114 9862-9871.

[19] Bender ML. Cyclodextrin Chemistry. Komiyama M. (Eds.), Berlin: Springer-Verlag; 1978.

[20] Bender ML, Komiyama M. Cyclodextrin Chemistry, Berlin: Springer Verlag; 1978.

[21] Rekharsky MV, Inoue Y. Complexation Thermodynamics of Cyclodextrins. Chem. Rev. 1998; 98 1875-1918.

[22] Khalafi L, Rohani M, Afkhami A. Acidity Constants of Some Organic Acids in the Presence of β-Cyclodextrin in Binary Ethanol–Water Mixtures by Rank Annihilation Factor Analysis. J. Chem. Eng. Data. 2008; 53 2389-2392.

[23] Ogoshi T, Harada A, Chemical Sensors Based on Cyclodextrin Derivatives. Sensors, 2008; 8 4961-4982.

[24] Kuwabara T, Nakamura A, Ueno A, Toda F. Inclusion Complexes and Guest-Induced Color Changes of pH-Indicator-Modified β-Cyclodextrins. J. Phys. Chem. 1994; 98 6297-6303.

[25] Ueno A, Kuwabara T, Nakamura A, Toda F. A Modified Cyclodextrin as a Guest Responsive Color-Change Indicator. Nature, 1992; 356 136-137.

[26] Kuwabara T, Takamura M, Matsushita A, Ikeda H, Nakamura A, Ueno A, Toda F. Phenolphthalein-Modified β-Cyclodextrin as a Molecule-Responsive Colorless-to-Color Change Indicator. J. Org. Chem., 1998; 63 8729-8735.

[27] Kuwabara T, Aoyagi T, Takamura M, Matsushita A, Nakamura A, Ueno A. Heterodimerization of Dye-Modified Cyclodextrins with Native Cyclodextrins. J. Org. Chem., 2002; 67 720-725.

[28] Tutaj B, Kasprzyk A, Czapkiewicz J. The Spectral Displacement Technique for Determining the Binding Constants of β-Cyclodextrin-Alkyltrimethylammonium Inclusion Complexes. J. Incl. Phenom. Macrocyclic Chem. 2003; 47 133-136.

[29] Meier MM, Bordignon Luiz MT, Farmer PJ, Szpoganicz B. The Influence of β- and γ -Cyclodextrin Cavity Size on the Association Constant with Decanoate and Octanoate Anions. J. Incl. Phenom. Macrocyclic Chem. 2001; 40 291-295.

[30] Cadena PG, Oliveira EC, Araujo AN, Montenegro MCBSM, Pimentel MCB, Lima Filho JL, Silva VL. Simple Determination of Deoxycholic and Ursodeoxycholic Acids by Phenolphthalein- β-Cyclodextrin Inclusion Complex. Lipids, 2009; 44 1063-1070.

[31] Skoulika SG, Georgiou CA, Polissiou MG. Interaction of β-Cyclodextrin with Unsaturated and Saturated Straight Chain Fatty Acid Anions Studied by Phenolphthalein Displacement. J. Incl. Phenom. Macrocyclic Chem. 1999; 34 85-96.

[32] Sasaki KJ, Christian SD, Tucker EE. Use of Visible Spectral displacement Method to Determine the Concentration of Surfactants in Aqueous Solution. J. Colloid Interface Sci, 1990; 134 412-416.

[33] Afkhami A, Madrakian T, Khalafi L. Flow Injection and Batch Spectrophotometric Determination of Ibuprofen Based on Its Competitive Complexation Reaction with Phenolphthalein- β-Cyclodextrin Inclusion Complex. Anal. Lett, 2007; 40 2317-2328.

[34] Afkhami A, Madrakian T, Khalafi L. Spectrophotometric Determination of Fluoxetine by Batch and Flow Injection Methods. Chem. Pharm. Bull. 2006; 54 1642-1646.

[35] Kuwabara T, Nakamura A, Ueno A, Toda F. Supramolecular Thermochromism of a Dyeappended β-Cyclodextrin. J. Chem. Soc., Chem. Commun. 1994; 689-690.

[36] Aoyagi T, Nakamura A, Ikeda H, Ikeda T, Mihara H, Ueno A. Alizarin Yellow-Modified β-Cyclodextrin as a Guest-Responsive Absorption Change Sensor. Anal. Chem. 1997; 69 659-663.

[37] Afkhami A, Khalafi L. Investigation of the Effect of Inclusion Erichrome Black T with β-Cyclodextrin on its Complexation Reaction with Ca^{2+} and Mg^{2+} using Rank Annihilation Factor Analysis. Supramol. Chem. 2008; 19 579-586.

[38] Nicolis I, Coleman AW, Selkti M, Villain F, Charpin P, Rango C. Molecular Composites Based on First-Sphere Coordination of Calcium Ions by a Cyclodextrin. J. Phys. Org. Chem., 2001; 14 35-37.

[39] Klufers P, Schuhmacher J. Sixteenfold Deprotonated γ-Cyclodextrin Tori as Anions in a Hexadecanuclear Lead(II) Alkoxide. Angew. Chem. Int. Ed. Engl., 1994; 33 1863-1865.

[40] Cucinotta V, Grasso G, Pedotti S, Rizzarelli E, Vecchio G, Blasio B, Isernia C, Saviano M, Pedone C. A Platinum (II) Diamino-β-cyclodextrin Complex: A Crystallographic and Solution Study. Synthesis and Structural Characterization of a Platinum(II) Complex of 6A,6B-Diamino-6A,6B-dideoxycyclomaltoheptaose. Inorg. Chem., 1996; 35 7535-7540.

[41] Yamamura H, Yotsuya T, Usami S, Iwasa A, Ono S, Tanabe Y, Iida D, Katsuhara T, Kano K, Uchida T, Araki S, Kawai M. Primary hydroxy-modified cyclomaltoheptaose derivatives with two kinds of substituents. Preparation of 6I-(benzyloxycarbonylamino)-, 6I-(tert-butoxycarbonylamino)- and 6I-azido-6I-deoxy-6II,6III,6IV, 6V, 6VI,6VII-hexa-O-tosylcyclomaltoheptaose and their conversion to the hexakis-(3,6-anhydro) derivatives. J. Chem. Soc., Perkin Trans 1 1998; 1299-1304.

[42] Suresh P. Abulkalam Azath I, Pitchumani K. Naked-Eye Detection of Fe^{3+} and Ru^{3+} in Water: Colorimetric and Ratiometric Sensor Based on per-6-amino-β-cyclodextrin/p-nitrophenol. Sens. Actuators, B 2010; 146 273-277.

[43] Alston DR, Slawin AMZ, Stoddart JF, Williams DJ. Cyclodextrins as Second Sphere Ligands for Transition Metal Complexes-The X-Ray Crystal Structure of [Rh(cod) $(NH_3)_2$ α-cyclodextrin][PF_6] $6H_2O$. Angew. Chem. Int. Ed. Engl., 1985; 24 786-787.

[44] Nicolis I, Coleman AW, Charpin P, Rango C. A Molecular Composite Containing Organic and Inorganic Components-A Complex from β-Cyclodextrin and Hydrated Magnesium Chloride. Angew. Chem. Int. Ed. Engl., 1995; 34 2381-2383.

[45] Stoddart JF, Zarzycki R. Cyclodextrins as Second-Sphere Ligands for Transition Metal Complexes. Recl. Trav. Chim. Pays-Bas, 1988; 107 515-528.

[46] Navaza A, Iroulapt MG, Navaza J. A Monomeric Uranyl Hydroxide System Obtained by Inclusion in the β-Cyclodextrin Cavity. J. Coord. Chem., 2000; 51 153-168.

[47] Odagaki Y, Hirotsu K, Higuchi T, Harada A, Takahashi S. X-Ray structure of the α-cyclodextrin–ferrocene (2 : 1) inclusion compound. J. Chem. Soc., Perkin Trans., 1990; 1 1230-1231.

[48] Tabushi I, Shimizu N, Sugimoto T, Shiozuka M, Yamamura K. Cyclodextrin Flexibly Capped with Metal Ion. J. Am. Chem. Soc., 1977; 99 7100-7102.

[49] Klingert B, Rihs G. Molecular encapsulation of transition metal complexes in cyclodextrins. Part 3. Structural consequences of varying the guest geometry in channel-type inclusion compounds. J. Chem. Soc., Dalton Trans1., 1991; 2749-2760.

[50] Bonomo RP, Blasio B, Maccarrone G, Pavone V, Pedone C, Rizzarelli E, Saviano M, Vecchio G. Crystal and Molecular Structure of the [6-Deoxy-6-[(2-(4-imidazolyl)ethyl)amino]- cyclomaltoheptaose]copper(II) Ternary Complex with l-Tryptophanate. Role of Weak Forces in the Chiral Recognition Process Assisted by a Metallocyclodextrin. Inorg. Chem., 1996; 35 4497-4504.

[51] Hoshino T, Ishida K, Irie T, Hirayama F, Uekama K. Reduction of Photohemolytic Activity of Benoxaprofen by β-Cyclodextrin Complexations. J. Incl. Phenom., 1988; 6 415-423.

[52] Hirayama F, Kurihara M, Uekama K. Improvement of Chemical Instability of Prostacyclin in Aqueous Solution by Complexation with Methylated Cyclodextrins. Int. J. Pharmaceut., 1987; 35 193-199.

[53] Gorecka BA, Sanzgiri YD, Bindra DS, Stella VJ. Effect of SBE4-β-CD, a Sulfobutyl Ether β-Cyclodextrin, on the Stability and Solubility of O6-Benzylguanine (NSC-637037) in Aqueous Solutions. Int. J. Pharmaceut., 1995; 125 55-61.

[54] Afkhami A, Khalafi L. Application of Rank Annihilation Factor Analysis to the Determination of the Stability Constant of the Complex XL and Rate Constants for the Reaction of X and XL with the Reagent Z using Kinetic Profiles. Bull. Chem. Soc. Jpn. 2007; 80 1542-1548.

[55] Afkhami A, Khalafi L. Spectrophotometric Investigation of the Effect of β-Cyclodextrin on the Intramolecular Cyclization Reaction of Catecholamines using Rank Annihilation Factor Analysis. Anal. Chim. Acta, 2007; 599 241-248.

[56] Bortolus P, Monti S. Photochemistry in Cyclodextrin Cavities. Adv. Photochem. 1996; 21 1-133.

[57] Munoz de la Pena A, Rodriguez MP, Escandar GM. Optimization of the Room-Temperature Phosphorescence of the 6-Bromo-2-Naphthol–A-Cyclodextrin System in Aqueous Solution. Talanta, 2000; 51 949-955.

[58] Hamai S. Inclusion of 2-Chloronaphthalene by α-Cyclodextrin and Room-Temperature Phosphorescence of 2-Chloronaphthalene in Aqueous d-Glucose Solutions Containing α-Cyclodextrin. J. Phys. Chem. B, 1997; 101 1707-1712.

[59] Hayashita T, Yamauchi A, Tong AJ, Chan Lee J, Smith BD, Teramae N. Design of Supramolecular Cyclodextrin Complex Sensors for Ion and Molecule Recognition in Water. J. Incl. Phenom. Macrocyclic Chem. 2004; 50 87-94.

[60] Suzuki I, Ito M, Osa T, Anzai JI, Molecular Recognition of Deoxycholic Acids by Pyrene-Appended β-Cyclodextrin Connected with a Rigid Azacrown Spacer. Chem. Pharm. Bull. 1999; 47 151-155.

[61] Bortolus P, Marconi G, Monti S, Mayer B. Chiral Discrimination of Camphorquinone Enantiomers by Cyclodextrins: A Spectroscopic and Photophysical Study. J. Phys. Chem. A, 2002; 106 1686-1694.

[62] Xu YF, McCarroll ME. Determination of Enantiomeric Composition by Fluorescence Anisotropy. J. Phys. Chem. A, 2004; 108 6929-6932.

[63] Corradini R, Dossena A, Galaverna G, Marchelli R, Panagia A, Sartor G. Fluorescent Chemosensor for Organic Guests and Copper(II) Ion Based on Dansyldiethylenetriamine-Modified β-Cyclodextrin, J. Org. Chem., 1997; 62 6283-6289.

[64] Fourmentin S, Surpateanu GG, Blach P, Landy D, Decock P, Surpateanu G. Experimental and Theoretical Study on the Inclusion Capability of a Fluorescent Indolizine β-Cyclodextrin Sensor Towards Volatile and Semi-volatile Organic Guest. J. Incl. Phenom. Macrocyclic Chem. 2006; 55 263-269.

[65] Surpateanu GG, Becuwe M, Catalin Lungu N, Dron PI, Fourmentin S, Landy D, Surpateanu G. Photochemical Behaviour Upon the Inclusion for Some Volatile Organic Compounds in New Fluorescent Indolizine β-Cyclodextrin Sensors. J. Photochem. Photobiol. Chem, 2007; 185 312-320.

[66] Liu Y, You CC, Wada T, InoueY. Molecular Recognition Studies on Supramolecular Systems. 22. Size, Shape, and Chiral Recognition of Aliphatic Alcohols by Organoselenium-Modified Cyclodextrins. J. Org. Chem., 1999; 64 3630-3634.

[67] Ikeda H, Li Q, Ueno A. Chiral Recognition by Fluorescent Chemosensors Based on N-Dansyl-Amino Acid-Modified Cyclodextrins. Bioorg. Med. Chem. Lett. 2006; 16 5420-5423.

[68] Pagliari S, Corradini R, Galaverna G, Sforza S, Dossena A, Montalti M, Prodi L, Zaccheroni N, Marchelli R. Enantioselective Fluorescence Sensing of Amino Acids by Modified Cyclodextrins: Role of the Cavity and Sensing Mechanism. Chem. Eur. J., 2004; 10 2749-2758.

[69] Khalafi L. Modified Cyclodextrins as Molecular Sensors. (Mini Review) Res. J. Chem. Environ. 2008; 12 102-103.

[70] Ikeda H, Nakamura M, Ise N, Oguma N, Nakamura A, Ikeda T, Toda F, Ueno A. Fluorescent Cyclodextrins for Molecule Sensing: Fluorescent Properties, NMR Characterization, and Inclusion Phenomena of N-Dansylleucine-Modified Cyclodextrins. J. Am. Chem. Soc., 1996; 118 10980-10988.

[71] Tong AJ, Yamauchi A, Hayashita T, Zhang ZY, Smith BD, Teramae N. Boronic Acid Fluorophore/β-Cyclodextrin Complex Sensors for Selective Sugar Recognition in Water. Anal. Chem., 2001; 73 1530-1536.

[72] Chen L, Dionysiou DD, Oshea K. Complexation of Microcystins and Nodularin by Cyclodextrins in Aqueous Solution, a Potential Removal Strategy. Environ. Sci. Technol., 2011; 45 2293-2300.

[73] Franco CM, Fente CA, Vazquez BI, Cepeda A, Mahuzier G, Prognon P. Interaction between Cyclodextrins and Aflatoxins Q1, M1 and P1: Fluorescence and Chromatographic Studies. J. Chromatogr. A. 1998; 815 21-29.

[74] Wei J, Okerberg E, Dunlap J, Ly C, Shear JB. Determination of Biological Toxins Using Capillary Electrokinetic Chromatography with Multiphoton-Excited Fluorescence. Anal. Chem., 2000; 72 1360-1363.

[75] Hashemi J, Asadi Kram G, Alizadeh N. Enhanced Spectrofluorimetric Determination of Aflatoxin B1 In Wheat by Second-Order Standard Addition Method, Talanta, 2008; 75 1075-1081.

[76] Ya-Qiong H, Xing-Chen L, Jun-Qiu L, Yu-Qing W. Association Mechanism of S-Dinitrophenyl Glutathione with Two Glutathione Peroxidase Mimics: 2, 2′-Ditelluro- and 2, 2′-Diseleno-bridged β-cyclodextrins, Molecules, 2009; 14 904-916.

[77] Qin XR, Abe H, Nakanishi H. NMR and CD Studies on the Interaction of Alzheimer Beta-Amyloid Peptide (12-28) with Beta-Cyclodextrin, Biochem. Biophys. Res. Commun., 2002 ; 297 1011-15.

[78] Yu L, Guo-Song Ch, Yong Ch, Fei D, Jing Ch. Cyclodextrins as Carriers for Cinchona Alkaloids: a pH-Responsive Selective Binding System, Org. Biomol. Chem., 2005; 3 2519-2523.

[79] Liu Y, Li L, Zhang HY, Fan Z, Guan XD. Selective Binding of Chiral Molecules of Cinchona Alkaloid by β- and γ-Cyclodextrins and Organoselenium-Bridged Bis(β-cyclodextrin)s, Bioorg. Chem., 2003; 31 11–23.

[80] Tewari BB, Beaulieu-Houle G, Larsen A, Kengne-Momo R, Auclair K, Butler, IS. An Overview of Molecular Spectroscopic Studies on Theobromine and Related Alkaloids, Appl. Spectrosc. Rev., 2012; 47 163–179.

[81] Sohajda T, Varga E, Ivanyi R, Fejos I, Szente L, Noszal B, Beni S. Separation of Vinca Alkaloid Enantiomers by Capillary Electrophoresis Applying Cyclodextrin Derivatives and Characterization of Cyclodextrin Complexes by Nuclear Magnetic Resonance Spectroscopy, J. Pharmaceut. Biomed. Anal. 2010; 531258–1266.

IntechOpen