Influence of Polar Solvents Upon the Complex Formation Between Crown Ethers and Cations in Nonpolar Medium

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Abbreviations, Formulae, and Indexes

12C4	12-crown-4
15C5	15-crown-5
18C6	18-crown-6
A	Affinity
b	slope
B12C4	Benzo-12-crown-4
B15C5	Benzo-15-crown-5
B18C6	Benzo-18-crown-6
c	Concentration of a chemical species [mol/L, g/L]
DB15C5	Dibenzo-15-crown-5
DB18C6	Dibenzo-18-crown-6
f	Activity coefficient
G	Free Enthalpy (J/mol)
H	Enthalpy (J/mol)
$\overline{H}$	Molar enthalpy (J/mol)
I	Ionic strength
k	Boltzmann constant (1.381×10^{-23} J/K)
k_A	Correction factor of activity coefficient
K_p, K_N	Mass action constant
l	The optical pathlength (cm)
[L]	Concentration of ligand L
L_1	3-[4-(1-aza-15-crown-5)-phenylazo]phthalhydrazide
L_2	N(benzo-15-crown-5)-3,5-dinitroanthranilic acid
m	Molality (mol/kg)
$[M^{n+}]$	Concentration of cations M^{n+}
$[ML^{n+}]$	Concentration of complexes ML^{n+}
N_A	Avogadro constant (6.023×10^{23} mol^{-1})
p	Pressure (bar)
Q	Heat (J)
r	Radius (Å)
R	Gas constant = 8314 J/(Kmol)
S	Entropie (J/Kmol)
t	Time (s)
T	Absolute temperature (K)
TOC	Total Organic Carbon
U	Sum of square errors
UV-Vis Spectrophotometry	Ultraviolet-Visible Spectrophotometry
V	Volume (L)
x	Molar fraction
α-CD	α-cyclodextrin
β-CD	β-cyclodextrin
γ-CD	γ-cyclodextrin
Δn	Number of moles of the complexes
ε	Dielectric constant
λ	Wavelength
μ	Chemical potential (J/mol)
ν	Stoichiometric coefficient

1 Introduction

1.1 Molecular Recognition

The central issue in supramolecular chemistry is molecular recognition, which consists in selective and strong binding of a guest molecule (substrate) by a given host molecule (receptor) [1]. Recognition in supramolecular chemistry is directed towards the field of molecular self-association to obtain supramolecular structures that are composed of many molecules as a result of noncovalent interactions. Based on the fundamental "lock-and-key" (Figure 1) steric fit concept introduced by *E. Fischer* in 1894 [2], the geometrical complementarity of shape, size, and functionality between the host and the guest molecule (Figure 2) was, in generally, accepted to be a major factor in molecular recognition [3, 4]. Biological reactions, such as immune response, enzyme catalysis, and signal transduction, involve specific recognition by macromolecules as proteins and they are the most characteristic processes of the living organisms.

P. Ehrlich introduced the concept of *receptor* ("*Corpora non agunt nisi fixata*") [5], and *A. Werner* [6] defined the term *coordination*, so that the supramolecular chemistry became a generalization of coordination chemistry [1]. The concept and the term of supramolecular chemistry were introduced in 1978 by *J.-M. Lehn* [7] who defined the supramolecular chemistry as "chemistry beyond the molecule", bearing on the organized entities of higher complexity that result from the association of two or more chemical species held together by intermolecular forces [8]. Supramolecular chemistry is an interdisciplinary field of science, which brings together knowledge from chemistry, physics, and biology. Complementarity, recognition, self-assembly, pre-organization, and self-replication are the basic operational concepts of supramolecular chemistry.

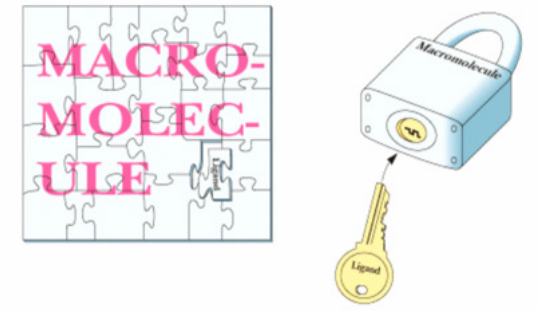


Figure 1: Puzzle versus "lock-and-key"concept [9].

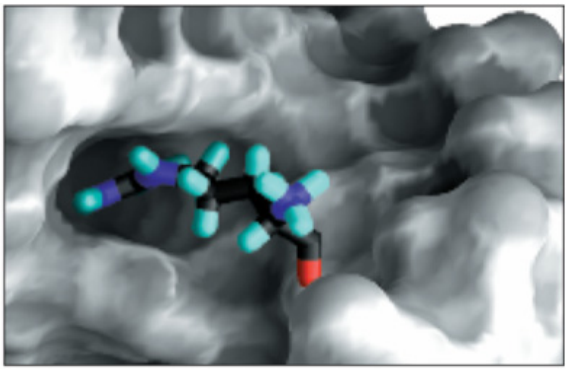


Figure 2: Complementary fit between a macromolecule and a small molecule [10].

Whereas molecular chemistry is based on the covalent bonds, supramolecular chemistry is based on noncovalent interactions, such as hydrogen bond, electrostatic forces, π-π stacking, charge-transfer, hydrophobic, Van der Waals, and coordination interactions (Figure 3) [1]. The molecular recognition of chemical or biological substrates by synthetic receptors is of current interest in supramolecular chemistry [1]. Molecular organization in living systems indicated that they are built from small building blocks and assembled into complex hierarchies of functional superstructures. The self-assembly of building blocks is another topic of interest in modern supramolecular chemistry, since many biological systems are constructed by self-assembly processes [11]. Self-assembly has provided an attractive means for constructing highly organized chemical entities [12, 13].

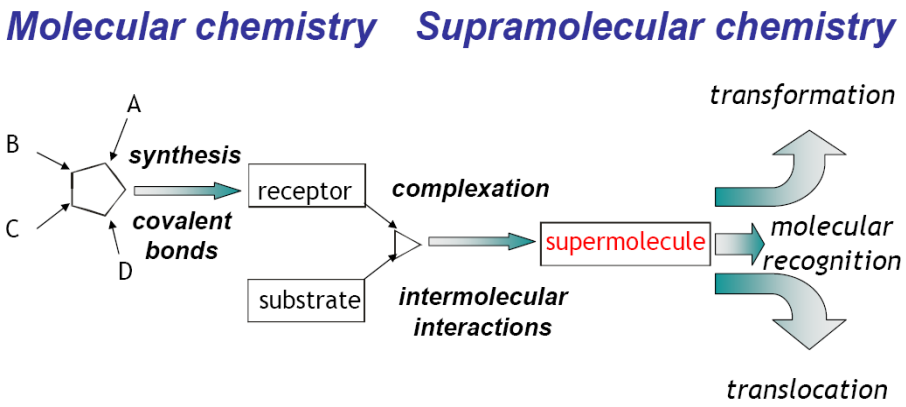


Figure 3: Schematics of molecular and supramolecular chemistry [1].

J.-M. Lehn has proposed the following definition of self-assembly: "… the evolution towards spatial confinement through spontaneous connection of a few/many components, resulting in the formation of discrete/extended entities at either the molecular, covalent or the supramolecular, noncovalent level" [1]. The self-assembly of the DNA double helix and protein quaternary structure are some relevant examples of biological process based on self-assembly [9]. The DNA double helix is formed upon self-assembly of two complementary helical strands. The driving forces for the formation of the DNA double helical arrangement are the establishment of H-bonds, π-π stacking of the base pairs and hydrophobic effects. Supramolecular synthesis, the building of complex supramolecular architecture, is based on combining molecules through noncovalent interactions [14, 15].

In 1967, C. J. Pedersen discovered the crown ethers [16, 17]. The cryptands (azapolyeters) were discovered by J.-M. Lehn [18] in 1969; they may envelop or encapsulate cations to make up extremely strong complexes called *cryptates*. The spherands developed by D. J. Cram [19] possess more elaborate structures than either crowns or cryptands. Like cryptands, spherand complexes are called *spherates* (Figure 4). Charles J. Pedersen, Jean-Marie Lehn, and Donald J. Cram received the Nobel Prize in Chemistry back in 1987 for developing the field of supramolecular chemistry.

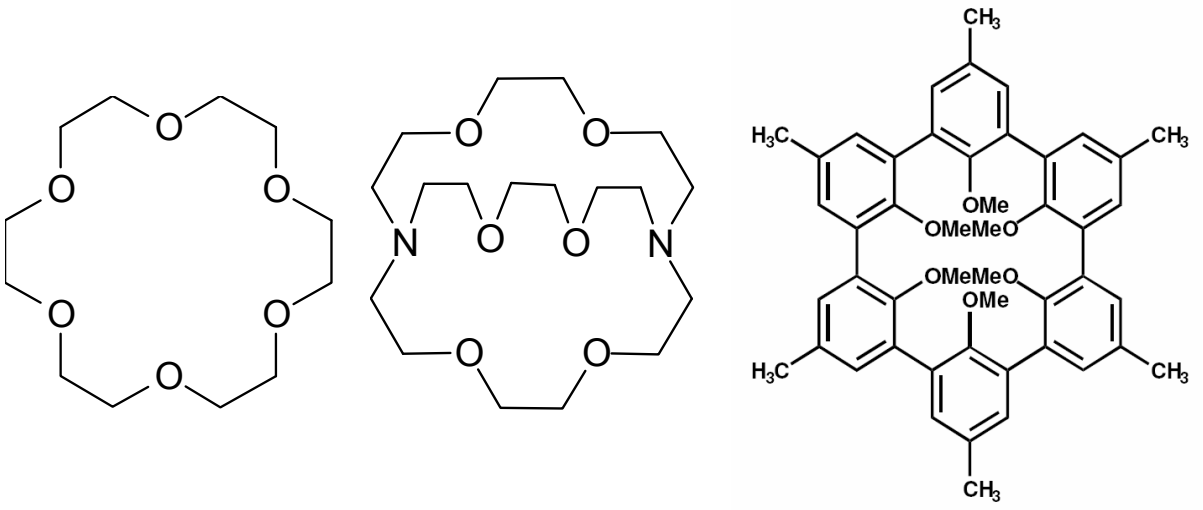


Figure 4: Crown ether (left), cryptand (center), and spherand (right).

Several factors must be taken into account in order to achieve high recognition by a receptor to a given substrate: (*a*) shape and size complementarity between receptor and substrate, (*b*) interactional complementarity, (*c*) large contact areas between receptor and substrate, (*d*) multiple interaction sites, (*e*) strong overall binding, and (*f*) medium effects [1, 20].

1.2 Noncovalent Interactions

Noncovalent interactions play a dominant role in chemical and biological world. Thus the folding of proteins into intricate three-dimensional forms, the specific recognition of substrates by enzymes, and the detection of signal molecules are characterized by noncovalent forces [1]. The noncovalent interactions are responsible for the function of synthetic or natural supramolecular complexes. Always reversible intermolecular noncovalent interactions are key elements in the design of molecular functionality [21-23].

Furthermore, these weak interactions are important synthetic tools in the preparation of complex molecular architectures. These kinds of complexes have a strong dependence not only on the molecular components they contain but also on the type of interactions which hold them together. Each of these interactions offers differences in strength, binding kinetics, and directionality. In this respect, the electrostatic interactions are strong, but not directional, in contrast, the hydrogen bonding is directional, but usually not strong enough to compete with multiple solvation effects in polar protic media [24].

Spectroscopic techniques, such as UV-Vis and NMR, calorimetric, potentiometric and microcalorimetric titrations, X-ray Langmuir (or Langmuir-Blodgett) techniques, and mass spectrometry were used to study the interactions occurring in host-guest complexes [25-27]. Several reports were focused on the characterization of noncovalent interactions involved in peptide-ligand complexes, protein-protein interaction, protein-ligand interaction, enzyme-substrat complexes or enzyme inhibitor complexes by different techniques [28, 29]. Nonetheless, the study of multiple interactions between host-guest complexes is of fundamental interest.

Electrostatic bonds, hydrogen bonds, van der Waals bonds, hydrophobic effects, cation-π interaction, π-π stacking, and charge-transfer are the most representative noncovalent interactions present in interactions of molecules or biomolecules. It is important to recognize that the precise control of the supramolecular systems, simple or sophisticated, is made possible not only by a single strong force or many weak forces working independently but through the directed cooperation of several and somewhat weak interactions, each of which is not strong enough to associate two molecules. Thus the chemical and biological molecular recognition phenomena may be unified as the chemistry of cooperative weak interactions.

Electrostatic bonds (ion-ion interactions, ion-dipol interactions, and dipole-dipole interactions). Molecules with dipole moments tend to orient themselves in the liquid and solid phases so that the negative end of one molecule is facing the positive end of another one [30]. The interactions of the permanent dipoles in different molecules are called *dipole-dipole interactions* [3].

Electrostatic bonds are governed by the Coulomb law, which explicitly express the interaction strength through the Coulombian force, *F* (in N), like:

$$F = \frac{1}{4\pi\varepsilon_r\varepsilon_0} \cdot \frac{q_1 q_2}{r^2} \tag{1.1}$$

where q_1 and q_2 are the charges (in C) of the two groups, r is the distance between their charge centers, $\varepsilon_0 = 8.85418\times10^{-12}\,\mathrm{C}^2/\mathrm{N}\cdot\mathrm{m}^2$ is the dielectric constant (or permittivity) of the vacuum, and ε_r is the relative dielectric constant of the medium (e.g., the solvent). The dielectric constant of the medium, $\varepsilon = \varepsilon_r\varepsilon_0$, has a large influence on the strength of the electrostatic interactions. Given the charges and the distance in between, the attraction is the strongest in vacuum ($\varepsilon_r = 1$), whereas in water ($\varepsilon_r = 78.5$ at 25°C) the attraction is the weakest. The *ionic bond, salt linkage, salt bridge*, or *ion pair* are some alternative names of this kind of electrostatic interactions [25].

Hydrogen bonds. These intermolecular interactions are the most widely used interactions in forming supramolecular structures and they can vary between few and hundreds of kJ/mol. In this kind of interaction, a hydrogen atom is shared by two other atoms. The atom to which the hydrogen is more tightly linked is called the hydrogen donor, whereas the other atom is the hydrogen acceptor [31-33]. The stability of hydrogen bonds depends on the basicity of the atom donors and acidity of the atom acceptors. In biological systems, the donor in a hydrogen bond is an oxygen or nitrogen atom that has a covalently attached hydrogen atom. The acceptor is either oxygen or nitrogen [9].

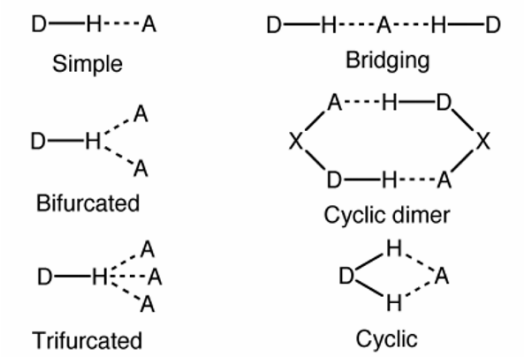


Figure 5: Examples of hydrogen bond types [13].

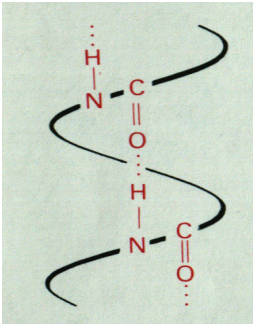


Figure 6: Hydrogen bonding between an amide and a carbonyl in an α-helix of a protein [9].

Hydrogen bonding is the most directional of the intermolecular interactions [13]. The degree of directionality depends on the donor polarity. In Figure 5, some examples of classical hydrogen bond types are shown. The hydrogen bonds are stronger than van der Waals bonds but much weaker than the covalent bonds. The α-helix of a protein is stabilized by hydrogen bonds between amide (– NH) and carbonyl (– CO) groups (Figure 6).

In DNA, the bases on opposite strands are held together by hydrogen bonds. In Figure 7a and Figure 7b, some examples of hydrogen bonds between nucleobases are presented. Since water is a major constituent of living organisms, an understanding of hydrogen bonding turns out to be of paramount importance. The strength of the hydrogen bond is reflected in the physical properties of compounds in which such bonding occurs, and depends on its microscopic environment [33].

Van der Waals bonds (*Dispersion and induction forces, 0.4-4.0 kJ/mol*). The weak forces that exist between nonpolar molecules are called van der Waals interactions. They are a collective group of inductive and dispersive intermoleculare forces. These interactions depend on

fluctuating induced dipoles and therefore on the sizes and shapes of covalent molecules. Even though the van der Waals interactions are weak, their additive effects (inductive and dispersive intramolecular forces) to complex formation is significant.

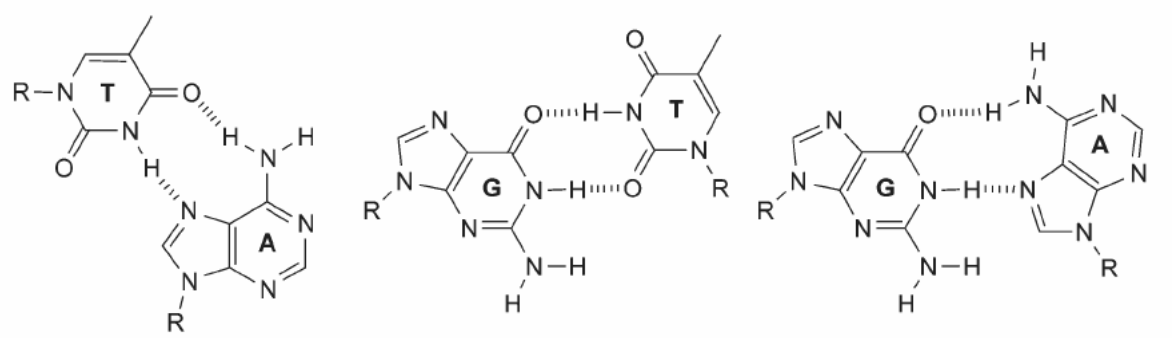


Figure 7a: Some examples of hydrogen bonds between nucleobases (G-guanine, A-adenine, T-tymine) [10].

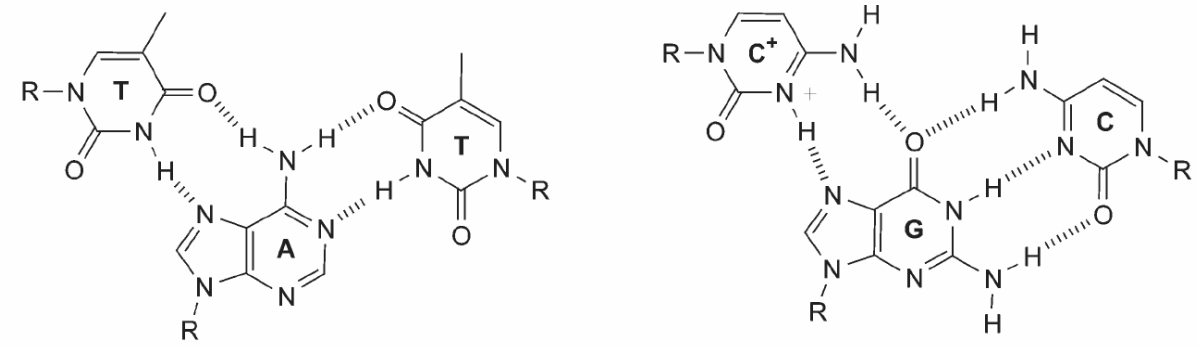
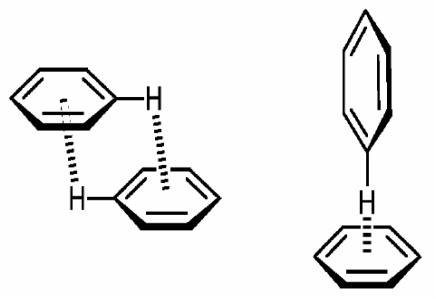


Figure 7b: Nucleobases-triplets [10].

The *inductive forces* are attractive and include permanent dipole-dipole and induced dipole-dipole interactions; their magnitude varies as an inverse power of the distance between the interacting species. *Dispersion forces* (London-Eisenschitz forces) result from momentary fluctuations of the weak dipoles like neighboring C–H bonds, which exceeds the permanent time-averaged moments and can assume an energetically favourable mutual orientation [25]. These forces rapidly fall off with r^{-6} between interacting bonds and, consequently, require an extremely good match between molecular surfaces.

π-π stacking interactions. This kind of interactions was observed in the crystalline structures of organic compounds containing aromatic moieties. Hunter and Sander proposed a simple model for treating these interactions based on electrostatic and van der Waals forces [34]. The π-π stacking interactions are directional and they are weaker than the hydrogen bonds. Two types of π-π stacking interactions are presented hereafter: *face-to-face* (Figure 8a) and *edge-to-face* (Figure 8b).



a **b**

Figure 8: Examples of π-π stacking interactions; *face-to-face* (a) and *edge-to-face* (b) [13].

The aromatic moieties possess a permanent negative potential above the plane which can exhibit a Coulomb-type attraction towards permanent full or partial changes. This is the basis of edge-to-face type of interaction. Such edge-to-face orientations between aromatic moieties are usually found in proteins [13]. Most host-guest systems are based on such interactions. They are also involved in stabilizing DNA through vertical base-pair interactions.

Cation-π interaction. These interactions act between cations and electroneutral acceptor parts such as π-electrons and lone pair electrons. The charge of the π-cloud is set off by the positive changes in the aromatic C-H bonds. Recently, many papers have reported that noncovalent *cation-π interaction* play an important role in building up the structure of many biological important macromolecules and in promoting fundamental functions like recognition, transport and chemical transformation of a substrate [26]. By computational studies it was suggested that the cation-π interaction may be responsible for the ion selectivity in potassium channels [35].

Charge-transfer interactions. These interactions are also known as *electron donor acceptor interactions* [13, 25] and they are very weak intermolecular forces. They may show up when good electron donors and acceptors are in close proximity. Then electrons from high energy occupied molecular orbitals of electron-rich compounds (*donors*) are transferred into low energy unoccupied orbitals of electron-poor systems (*acceptors*). This aspect is recognized by distinct charge-transfer transitions in the UV-Vis spectral region [36]. The stabilization of interacting π-systems is frequently explained by using charge-transfer interactions. The solvation effects play an important role in the strength of host-guest binding in such systems.

Hydrophobic/solvatophobic interactions (<40 kJ/mole). Nonpolar molecules, or groups, tend to associate in water; in other words, they tend to cluster together in associations called hydrophobic attractions. As a matter of fact, nonpolar organic compounds avoid water and prefer a nonpolar environment. Whereas hydrogen bonds and van der Waals forces relate primarily to enthalpic factors, hydrophobic effects relate primarily to entropic factors. Moreover, the entropic factors mainly concern the solvent not the solute [37].

These interactions are of importance in many chemical and biochemical processes. In this respect, the hydrophobic attractions are a major driving force in folding of macromolecules, the binding of substrates to enzymes, and the formation of membranes that define the boundaries of cells and their internal compartments. It is well known that hydrophobic interactions constitute an important factor in the stability of the folded structure of water-soluble proteins [4].

1.3 Host-Guest Complexation

Macrocyclic ligands are able to form stable and selective complexes with appropriate substrates by hydrogen bonds, ionic interaction, and/or hydrophobic interactions. Selective complexation of guest compounds by host molecules based on noncovalent interactions is one of the fundamental issues in supramolecular chemistry (Figure 9).

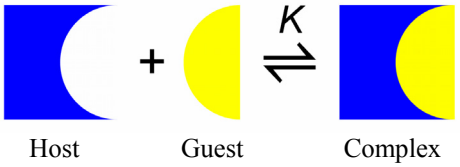
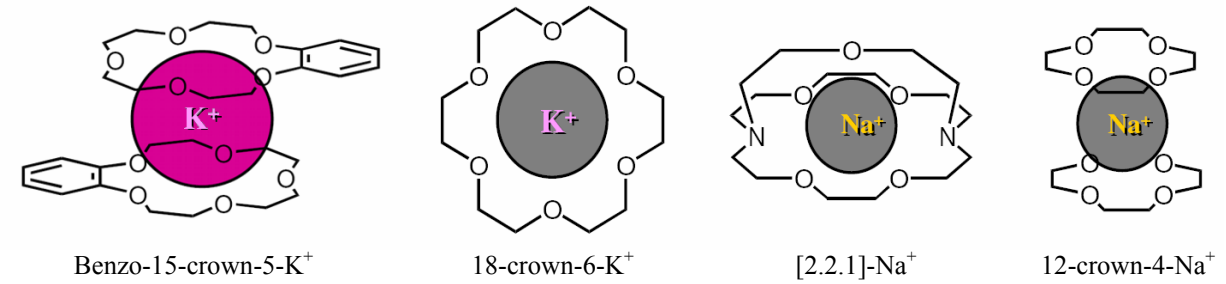


Figure 9: Host-guest complexation.

Noteworthy, the type, the shape, and the flexibility of both the host and the guest have the strongest influence on the complex stability [26]. The geometry of the complex and the fit (or misfit) between various guests and a specific host are of particular importance concerning the selective stabilization or selective destabilization of specific complexes (Figure 10) [38, 39]. Likewise, the solvent dependence plays an important role in determining the complexation strength.

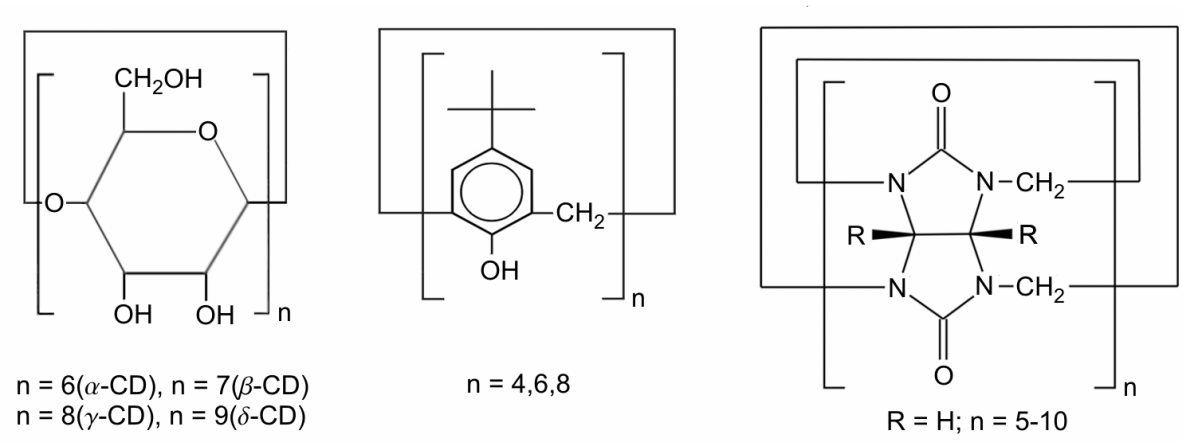
Reinhoudt *et al.* [40] defined *multivalency* as a potential self-assembly tool in supramolecular chemistry and nanoscience that confers unique thermodynamic and kinetic behaviour to supramolecular complexes. Moreover, this multivalency describes the binding of two (or more) entities that involves the simultaneous interaction between multiple complementary functionalities on these entities. One of the most studied types of multivalent systems consists of pseudorotaxanes made up from crown ethers and charged ammonium-based cationic guests [41].



Benzo-15-crown-5-K^+ 18-crown-6-K^+ [2.2.1]-Na^+ 12-crown-4-Na^+

Figure 10: Complexes of some cations with macrocycles [38].

Cyclodextrins [42], calix[n]arenes [43, 44], and cucurbit[n]urils [45-58] are one of the most important category of hosts for supramolecular assemblies (Figure 11), along with crown ethers, cryptands, and spherands. These receptors have the possibility to form interesting complexes with both metal cations and biologically relevant compounds by exhibiting extractability and selectivity.



n = 6(α-CD), n = 7(β-CD)
n = 8(γ-CD), n = 9(δ-CD)

n = 4,6,8

R = H; n = 5-10

Figure 11: Structures of cyclodextrins (left), calix[n]arenes (center), and cucurbit[n]urils (right).

The macrocyclic receptors as host compounds may be classified in two main groups: (*i*) host molecules that have a shape that enables the accommodation of a guest molecule such as polyethers, cyclodextrins, cyclophanes, and calixarenes, and (*ii*) host molecules that can form inclusion through packing in a lattice in such a way that cavities, channels, or layers are being

occupied by guest molecules. The inclusion compounds obtained from the first type of host molecules are also called “cavitates” and the inclusion compounds obtained from the second type of host molecules are also called “clathrates” [59]. The channel clathrates are very attractive due to their potential applications in separation between guest molecules.

Considerable work has been devoted to the design and synthesis of molecular receptors that mimic the natural binding sites for hormones, neurotransmitters, and other biologically relevant guests. The diversity in receptor design allows several applications in various fields. Recently, a current trend in chemical sciences has consisted in building up multivalent, multifunctional macromolecular receptors. Synthetic receptors have become more sophisticated with concave surface, such as clefts [60], armatures [61], tweezers [62], bowls [63], and other shapes [64]. The using of the aggregates of self-complementary compounds rather than one large molecule as a receptor was a challenge for the researchers in recent years [65, 66]. Another milestone in the design and synthesis of receptors was the obtaining of heteroditopic receptors, which were able to simultaneously complex cations and anions, either as ion-pairs or as free ions [67]. These kinds of receptors can exhibit interesting allosteric or cooperative effects, which improve the selective extraction of salts in organic media or their transport through artificial membranes.

A large diversity can be generated through the combination of a few components, and a vast library of multicomponent species can be developed. J.-M. Lehn [1, 68, 69] has pioneered the field of dynamic combinatorial chemistry, in which the composition of equilibrating libraries of molecular receptors is trained by the presence of the desired target. Nowadays, combinatorial chemistry offers elegant means to design and subsequently obtain by synthesis some chemical compounds having directed structural design in terms of their physicochemical properties and application-oriented.

1.4 Crown Ethers

Since their discovery by C. J. Pedersen [16, 17], the crown ethers (Figure 12) have proved to be extremely useful macrocyclic receptors for complexation of various organic, inorganic, or biological compounds, such as proteins and DNA. The complexation of cations by crown ethers has been extensively studied [70, 71]. Basically, crown ethers form two-dimensional complexes as depicted in some examples (Figure 10). Crown ethers interact strongly with alkali metal cations by charge-dipole interactions. Even though most of the complexation studies on crown ethers involve metal ions, several other guest compounds, such as ammonium ion (NH_4^+) and primary alkylammonium (RNH_3^+), have also been examined [72, 73]. The NH_4^+ ion differs from alkali metal ions by offering directionality. This feature confers a particularity of studies involving in ammonium ion complexation. Three $N-H\cdots O$ hydrogen bonds can form to alternating oxygen atoms in 18-crown-6 ring concerning the primary ammonium ions complexation (Figure 13). The binding arrangement of an ammonium ion and 18-crown-6 has been observed in gas phase [74, 75] and in solid state structures [76] as well.

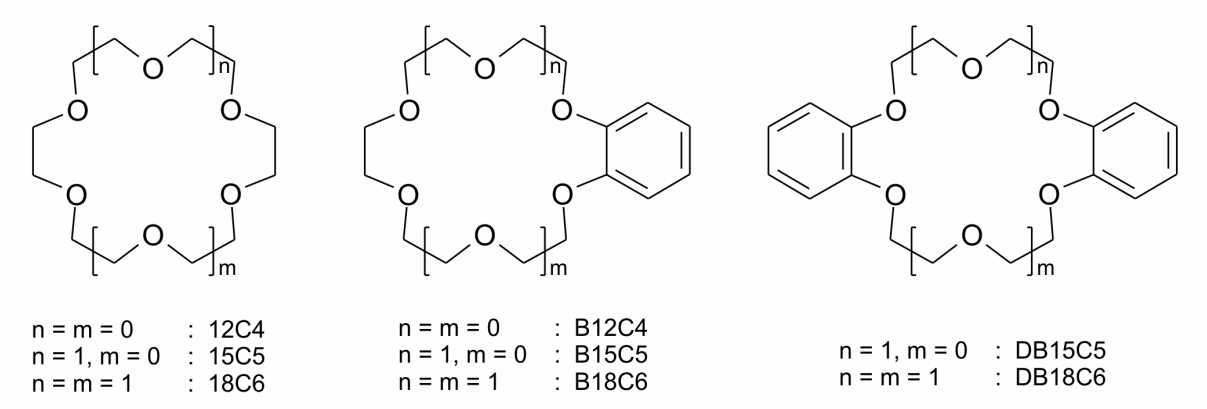


Figure 12: Crown ethers.

Water, endowed with two OH donors available for H-bonding, may also complex within a macrocycle. Goldenberg [76] found that one of Cram's bis(binaphtyl) crowns [77] included water and Newkome *et al*. [78] obtained the solid-state structure of a pyrido-18-crown-6 diester in which water is placed, as in the aza-18-crown-6·HCl complex [79] at the center of the macroring (Figure 14).

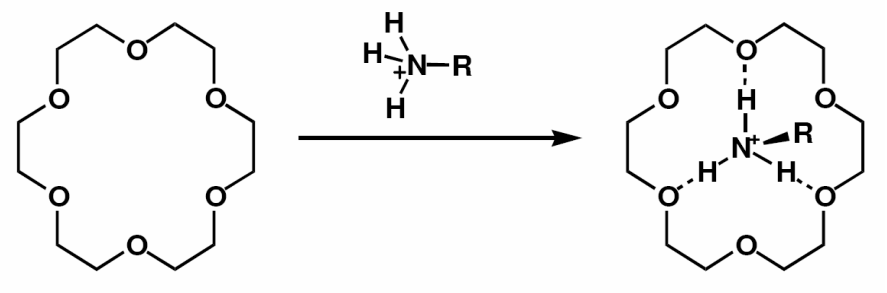


Figure 13: Ammonium complex formation by 18-crown-6.

The presence of benzo groups in the structure of simple crown ether rigidifies the crown and reduces the donor property of the attached oxygen atoms. It is the case of benzo-crown ethers. The ion size, geometry, solvation or coordination number, and charge density are some factors that influence the ion recognition by crown ethers.

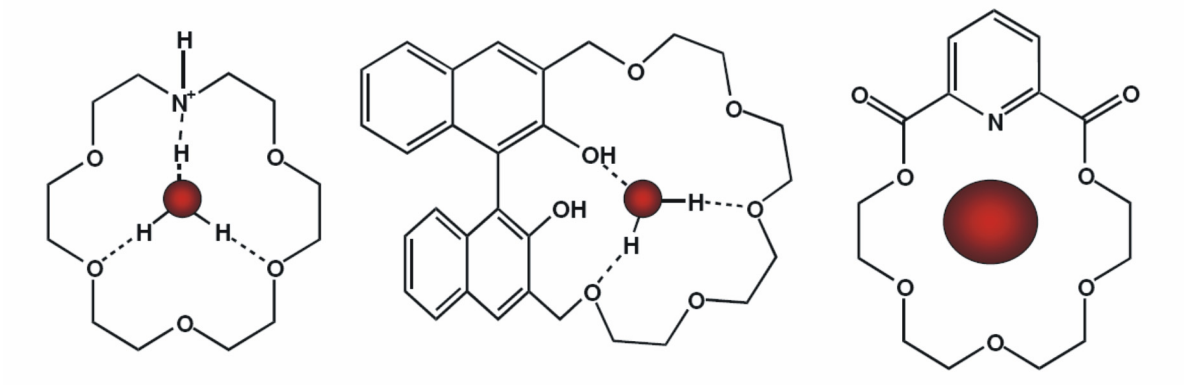


Figure 14: Crystal structures of water complexes with different crown ethers [39].

Crown ethers have been extensively explored both from the point of view of imitating and understanding various biological processes and from the point of view of synthesizing more efficient and selective receptors alike [39]. The scientific community has started up an impressive activity of preparation novel macrocycles, to establish the limits of crown ether's structure, and to assess the range of their biological and chemical properties. A large number of derivatives were prepared and their complexation properties were studied. They interact with enzymes in organic solvents. Also, it is known that 18-crown-6 and 15-crown-5 aid the solubilization of proteins in organic solvents [80]. On the other hand, crown ethers can enhance the catalytic activity and the enantioselectivity of enzymes in certain instances [81, 82].

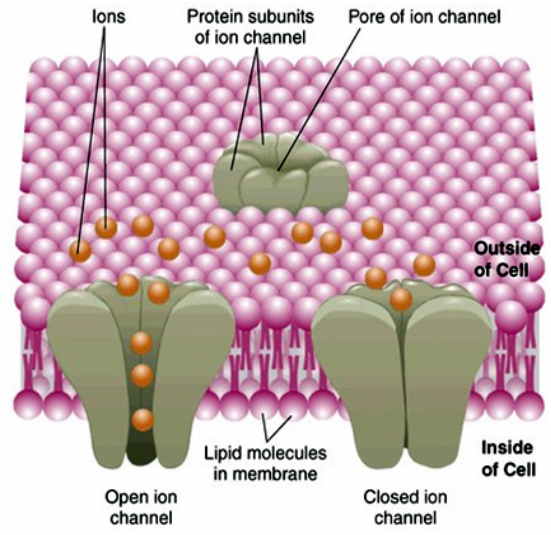


Figure 15: Ion channel system.

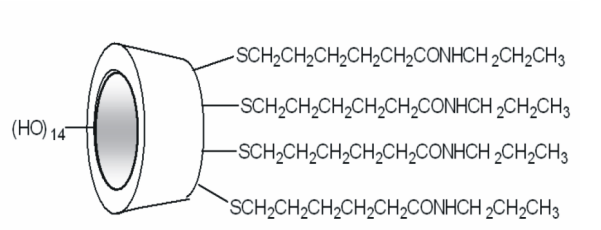


Figure 16: Synthetic channel of Tabushi *et al*. [86].

The development of synthetic, ion channel models that conduct protons and sodium cation or chloride anion in phospholipid bilayer membrane (Figure 15) involving crown ethers has been the subject of many studies [83-85]. It is known the pioneering studies of tetrachained cyclodextrin channel of Tabushi (Figure 16) [86, 87]. The 2003 Nobel Prize in chemistry was awarded for the studies concerning the structures of ion channels. It is well known that crown ethers interact with the most relevant cations from biology namely H^+, Na^+, K^+, and Ca^{2+}. Representative studies concerning the crown ether-based channels are the "chundles" reported by Lehn [88], the bola-amphiphiles of Fyles [89, 90], Nolte's polymerized isonitriles [91], Voyer's crown-substituted peptides [92] the redox-switchable systems of Hall [93] and the steroid-substituted crowns of Pechulis *et al*. [94].

In this respect, Gokel *et al.* [95, 96] elaborated the studies concerning the cation channels based on crown ethers (Figure 17) and the anion channels based on synthetic peptides. They have developed the channels that will selectively transport cations (H^+, Na^+, K^+) and small molecular species through membranes having specific compositions.

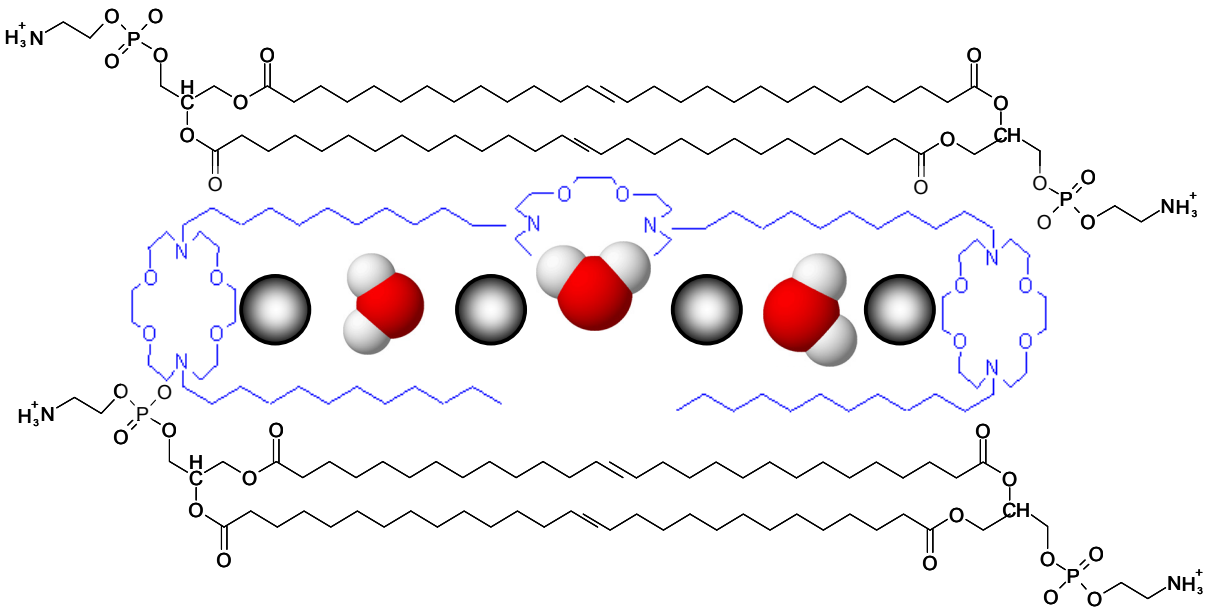


Figure 17: An artificial ion channel [95].

Such compounds will have therapeutic applications like antibiotic activity in the cation channel compounds or using the chloride channels as potential therapeutic agents for the treatment of cystic fibrosis. It should be mentioned that crown ethers became important compounds as scaffold concerning the development of novel and complex systems that model natural structures and processes.

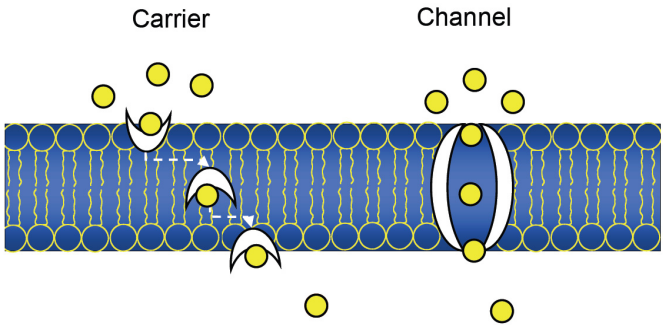


Figure 18: Transport mechanisms through a membrane.

To conclude with, apart from their specific complexation properties, the crown ethers may play the role of carriers and ion channels through membranes (Figure 18).

1.5 Cryptands

It is known that the most remarkable property of crown ethers and cryptands is their ability to bind various species. Cryptands were reported for the first time by Lehn who suggested the name of cryptand from the Greek *kryptos* which means *hidden* [18]. According to the data presented in the literature, cryptands (Figure 19) form stronger complexes with cations than crown ethers do [1, 97, 98]. This is due to a larger encapsulation of the cation by the donor group chains [39]. Cryptands usually can be considered three-dimensional binders because the three donor group-containing chains form a symmetrical array about an appropriately sized cation. Such an example of appropriate size is the complex of [2.2.1] ($r = 1.1$ Å) with Na^+ ($r = 1.02$ Å) presented in Figure 10.

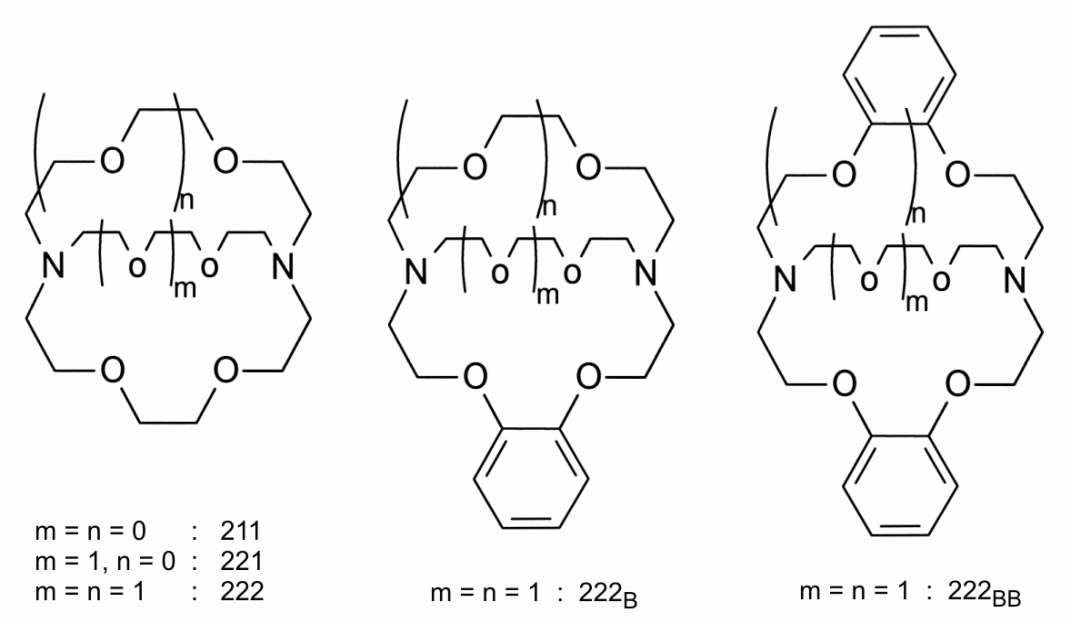


Figure 19: Cryptand family.

Because of their spheroidal cavity, cryptands are adequate for binding the spherical alkali cations and alkaline-earth cations. Cryptates of alkali and alkaline-earth cations have stabilities higher than those of either the natural or synthetic macrocyclic ligands. The selectivity of cryptate formation depends on the size complementarity between the cation and the intramolecular cavity, the so-called *spherical recognition* [1]. In the last time, positively charged cryptands, typically the N-donor azacryptands, were synthesized and their binding properties towards anions were estimated [99].

1.6 Cyclodextrins

Cyclodextrins were discovered in 1891 by Villiers [100] and their preparation and isolation was first performed back in 1903 by Schardinger [101]. Cyclodextrins are obtained from degradation of starch by the enzyme cyclodextrin transglycosylase [102]. Cyclodextrins are cyclic molecules built from D-glucose units (Figure 20): six (α-cyclodextrin), seven (ß-cyclodextrin), and eight (γ-cyclodextrin) linked together via α-(1-4) bonds with the cavity diameters in the range of 4.7-5.3 Å for α- CD, 6.0-6.5 Å for β-CD, and 7.5-8.3 Å for γ-CD) [103]. All hydroxyl groups of the D-glucose are located outside the cavities of cyclodextrins and the interior is considered as a largely apolar binding site. The structure of cyclodextrins

were studied in the solid state and in solution as well. Saenger [102, 104] made important contributions in elucidating the structure of cyclodextrins and their complexes.

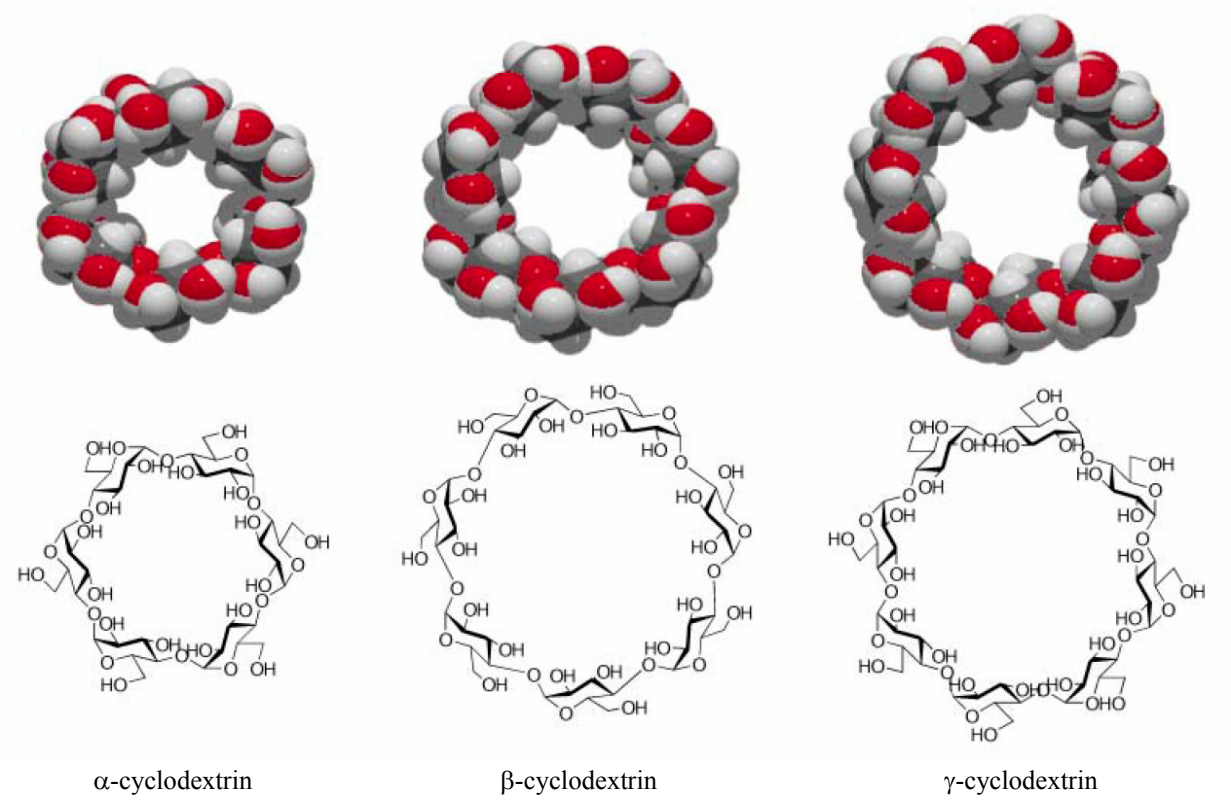


Figure 20: The structures of 3 different cyclodextrins (bottom) and their space filling models (top) [103].

Cyclodextrins have a hydrophilic exterior and a hydrophobic cavity, which is able to form host-guest inclusion complexes with a large variety of guest compounds as a function of size, shape, and hydrophobicity of both the cyclodextrin and the guest compound [105-115]. The steric factors are also important, in formation and stability of cyclodextrin inclusion complexes. The principal driving forces involved in inclusion complexation of cyclodextrins are weak interactions, such as electrostatic interactions, hydrophobic effects, and van der Waals interactions, determined by a combination of various factors. Hydrogen bonding is also involved in some complexes. The best fit between the guest molecules and the cavity of the cyclodextrins also has a pronounced influence upon the stability of the complex formed [116-118]. The structure of cyclodextrin inclusion complexes as well as the catalytic mechanisms of cyclodextrin have been thoroughly investigated [117].

Therefore, for a better understanding of the mechanism and factors that are responsible for controlling the complex formation by weak interactions, the thermodynamic data were intensively investigated for a variety of charged or uncharged compounds, including biologically-active substances and α-, ß-, and γ-cyclodextrins [119]. These inclusion compounds are models of interest in the study of noncovalent receptor-ligand complexes. There are numerous studies dedicated to the experimental techniques used for investigation of inclusion complexes, such as NMR measurements, calorimetric or microcalorimetric titrations, potentiometric titrations, mass spectrometry, and ultrasonic measurements [100, 120-123].

Cyclodextrins have the ability of forming diastereomeric supramolecules assemblies. This property confers to cyclodextrins the possibility to be used for enantioseparations. The stereoselectivity of cyclodextrins by complexation was discovered by Cramer (1952) [124]. Therefore, cyclodextrins have the ability to separate not only molecules with different size or shape, but also to differentiate between optical antipodes.

Due to their ability to form complexes with biologically important metabolites and pharmaceuticals as well as with compounds of environmental importance, cyclodextrins are considered to be important building blocks for design of various supramolecular devices and materials which mimic biological activities and functions [125-127]. Various kinds of derivatives of cyclodextrins were prepared, such as anhydro derivatives, lipophilic derivatives, amphilic derivatives (by self-organizable properties), rotaxanes, polyrotaxanes, and catenanes [106, 128].

The modified cyclodextrins were used as artificial enzymes, in drug delivery systems, molecular devices, as well as molecular sensors [129, 130]. In contrast to crown ethers, cryptands, cyclophanes and calixarenes that are focused on molecular recognition of low molecular weight compounds, cyclodextrins are able to recognize and sensitively respond to larger and more complicated compounds and even polymers. It is known that in biological systems like enzymes-substrates, antigen-antibodies, DNA, RNA, and cell adhesion systems, the recognition of macromolecules by macromolecules plays an important role in constructing supramolecular structures and maintaining their lives [131].

In the product development of pharmaceutical industry, cyclodextrins are used as solubilizers, diluents, or as tablet ingredients for increasing the stability and bioavailability of drugs. In chemical industry cyclodextrins are used as catalysts, or catalyst additives, improving the selectivity of reactions in separation and purification procedures in industrial processes [104, 105]. Having the ability to solubilize hydrophobic compounds in water, cyclodextrins can be used as inverse phase-transfer catalysts. In the food and cosmetic industries, cyclodextrins have an important role in the stabilization of flavours and elimination of undesired tastes [132-135].

1.7 Physical Chemistry Background

1.7.1 Chemical Thermodynamics

Physics concerns with the mechanics of events in nature. Thermodynamics is the study of energy changes accompanying physical and chemical changes. The term itself clearly suggests what is happening: “thermo” from temperature, meaning energy, and “dynamics”, which means the change with time. Thermodynamics can be roughly encapsulated within five topics: (*i*) heat and work, (*ii*) energy, (*iii*) enthalpy, (*iv*) entropy, (*v*) free energy.

1.7.1.1 Thermodynamic potentials

(*i*) *Heat and Work*

Heat and work are both forms of energy; they are also related forms, in that one can be transformed into the other. In SI, heat energy is measured in Joules (J). The specific heat, *C*

(the heat required to raise one 1 gram of a material one degree Celsius), is generally defined as:

$$C = \frac{Q}{M \cdot \Delta T} \tag{1.2}$$

where:

C is the specific heat in J/Kmol
Q is the heat added in J
M is the mass in grams
ΔT is the rise in temperature of the material in degrees Celsius

Chemical work is primarily related to that of expansion. In physics, work is defined as:

$$W = (\text{distance}) \cdot (\text{force})$$

where:

W = work in J (1J = N·m)
distance is in meters (m),
force is in Newtons (1N = 1kg·m/s^2)

In chemical reactions, work is generally defined as:

$$W = (\text{distance}) \cdot (\text{area} \cdot \text{pressure})$$

The value of distance times area is actually the volume, V. It turns out that for a reaction taking place in a container of some volume, the work, dW, is given by pressure, p, times the change in volume, dV, in liters:

$$\Delta W = -p \cdot \Delta V \tag{1.3}$$

If $dV = 0$, then no work is done.

(*ii*) *Energy*

The first law of thermodynamics states that energy cannot be created or destroyed, it can only change form. In chemical terms, that means energy is converted to work, energy in the form of heat moves from one place to another, or energy is stored up in the constituent chemicals. Heat is defined as that energy that is transferred as a result of a temperature difference between a system and its surroundings:

$$\Delta U = \Delta Q + \Delta W \quad \text{or} \quad \Delta U = \Delta Q - p \cdot \Delta V \tag{1.4}$$

where:

dU is the change in internal energy of a system in J
Q is the heat flowing from the surroundings into the system in J
W is the work being done by the system in J

If $Q > 0$, the reaction is *endothermic* (the heat flows into the reaction medium from the outside surroundings), whereas if $Q < 0$, the reaction is *exothermic* (heat is given off to the external surroundings).

The internal energy of a system is a *function of state*, meaning a quantity whose value is independent of the past history of the system. Mathematically, all state functions are expressed by total differentials.

(*iii*) *Enthalpy*

Assume a chemical system that undergoes some change at fixed volume, then the heat output equals the change in internal energy, $Q = \Delta U$. The enthalpy change of a system, dH, is defined as being equal to its heat output at constant pressure:

$$\Delta H = Q \tag{1.5}$$

The enthalpy itself, as a state function, is defined as:

$$H = U + pV \tag{1.6}$$

where U is the energy of the system in Joules. *H*, *U* and *V* are functions of state; the change in enthalpy, ΔH, on going from the initial state to the final state is independent of the pathway and the rate of change:

$$\Delta H = H_{final} - H_{initial} = H(products) - H(reactants) \tag{1.7a}$$

Likewise, the change in enthalpy can be written differentially from eq. (1.6):

$$dH = dU + p \cdot dV + V \cdot dp \tag{1.7b}$$

Then from eq. (1.4) it results at constant pressure:

$$dH = Q + V \cdot dp \tag{1.7c}$$

This equation is the basis of an (isobaric) titration calorimetric experiment, in which by measuring the exchange of heat, *Q*, the change in enthalpy, dH, is directly obtained.

The thermodynamic state of a system is defined by a set of independent variables like:

$$H = H(T, p, \xi) \tag{1.8}$$

Since *H* is a function of state:

$$dH = \left(\frac{\partial H}{\partial T}\right)_{p,\xi} \cdot dT + \left(\frac{\partial H}{\partial p}\right)_{T,\xi} \cdot dp + \left(\frac{\partial H}{\partial \xi}\right)_{T,p} \cdot d\xi \tag{1.9}$$

From eqs. (1.5) and (1.9) it results

$$Q = dH = \left(\frac{\partial H}{\partial \xi}\right)_{T,p} \cdot d\xi \tag{1.10}$$

which gives the change in enthalpy for $d\xi$ extent of reaction at fixed temperature, *T*, and fixed pressure, *p*. The differential $d\xi$ generally describes the change produced by introducing δn_j^0 moles of chemical substance *j*. Dividing eq. (1.10) by dn_j^0, the fundamental equation governing the calorimetric titrations is obtained:

$$\frac{Q}{dn_j^0} = \left(\frac{\partial H}{\partial \xi}\right)_{T,p} \cdot \frac{d\xi}{dn_j^0} \tag{1.11}$$

(*iv) Entropy*

Entropy is a measure of the disorder of a system. Work must be done to keep the entropy of the system low. The second law of thermodynamics states that all systems tend to reach a state of equilibrium. It turns out that all spontaneous changes in an isolated chemical system occur

with an increase in entropy. Entropy, denoted by *S*, like *T*, *p*, *V*, and *H*, is a function of state and changes in entropy are calculated as:

$$\Delta S = S_{final} - S_{initial} = S(products) - S(reactants) \tag{1.12}$$

(*v*) *Free Enthalpy*

The free enthalpy (or Gibbs energy) of a system, denoted by *G*, is defined as the energy of a system that is free to do work at constant temperature and pressure:

$$G = H - TS \tag{1.13}$$

Free enthalpy is also a state function, so that

$$\Delta G = G(products) - G(reactants) \tag{1.14}$$

The second law of thermodynamics enforces the direction of any spontaneous change towards a lower free enthalpy *G* for chemical reactions in a system at fixed temperature and pressure. Assume that dn^0 moles of substance *M* are introduced into a system containing n^0 moles of solvent *L*. The spontaneous process between *M* and *L* is driven by the affinity *A* for the chemical reaction, producing a change in chemical composition, $d\xi$ (in moles), such as:

$$A \cdot d\xi \geq 0 \quad \text{(De Donder's inequality [136])} \tag{1.15}$$

This is the basic consequence of the second law. It comes out that:

$$dG = -A \cdot d\xi \tag{1.16}$$

which, formally, amounts to:

$$T \cdot dS = Q + A \cdot d\xi \tag{1.17}$$

The change in thermodynamic energy at pressure *p* and temperature *T* is obtained by combination of the first and second law of thermodynamics:

$$dU = T \cdot dS - p \cdot dV - A \cdot d\xi \tag{1.18}$$

Since, by definition,

$$G = H - TS = U + p \cdot V - T \cdot S \tag{1.19a}$$

then

$$dG = dU + dp \cdot V + p \cdot dV - dT \cdot S - T \cdot dS \tag{1.19b}$$

The combination of eqs. (1.17) and (1.18) yields:

$$dG = -S \cdot dT + V \cdot dp - A \cdot d\xi \tag{1.19c}$$

which, at constant *T* and *p*, reduces to eq. (1.15). It means that, when $dn^0(M)$ moles of substance *M* are introduced into a system of $n^0(L)$ moles of solvent *L*, the spontaneous chemical reaction proceeds until *G* reaches a minimum and *A* turns down to zero. Hence, at equilibrium:

$$A^{eq} = -\left(\frac{\partial G}{\partial \xi}\right)^{eq}_{T,p} = 0 \tag{1.20}$$

Further on, if a new quantity of substance is introduced in the system, then *G* increases and *A* departures from 0. Spontaneous chemical reactions proceed until *G* reaches a new minimum

and the affinity goes down to zero again, while the solution reaches a new equilibrium composition.

The thermodynamic potentials *G*, *H*, and *S* are macroscopic (extensive) properties of a solution. Yet the properties of chemical substances are more conveniently specified by the chemical potentials. For a solution containing solute *j* in water, its *chemical potential* μ_j is the differential change in Gibbs energy when a small amount of substance *j* is added at fixed *T* and *p*:

$$\mu_j = \left(\frac{\partial G}{\partial n_j} \right)_{T,p,n_1} \tag{1.21}$$

where n_j stands for the moles of solute and n_1 for the moles of water. An alternative simpler way to conceptualize the above expression invokes the volume *V* of a solution at temperature *T* and pressure *p* containing n_j moles of solute and n_1 moles of water, which is defined as a set of independent variables:

$$V = V\left(T, p, n_1, n_j\right) \tag{1.22}$$

By differentiation we obtain:

$$dV = \left(\frac{\partial V}{\partial T} \right)_{p,n_1,n_j} \cdot dT + \left(\frac{\partial V}{\partial p} \right)_{T,n_1,n_j} \cdot dp + \left(\frac{\partial V}{\partial n_1} \right)_{T,p,n_j} \cdot dn_1 + \left(\frac{\partial V}{\partial n_j} \right)_{T,p,n_1} \cdot dn_j \tag{1.23}$$

where the meaning of the partial derivatives are as follows:

$\left(\frac{\partial V}{\partial T} \right)_{p,n_1,n_j}$ the isobaric thermal expansion at constant composition;

$\left(\frac{\partial V}{\partial p} \right)_{T,n_1,n_j}$ the isothermal compression at constant composition;

$\left(\frac{\partial V}{\partial n_1} \right)_{T,p,n_j}$ the partial molar volume of water in the aqueous solution, V_1;

$\left(\frac{\partial V}{\partial n_j} \right)_{T,p,n_1}$ the partial molar volume of solute j in the aqueous solution, V_j.

It turns out that the volume for the aqueous solution containing the solute *j* is given by:

$$V = n_1 \cdot V_1 + n_j \cdot V_j \tag{1.24}$$

and its free Gibbs energy:

$$G = n_1 \cdot \mu_1 + n_j \cdot \mu_j \tag{1.25}$$

where μ_1 and μ_j are the chemical potentials of the solvent and solute, respectively.

In the context of complexation reactions between a ligand *L* and a metallic cation *M*, the following chemical equilibrium is assumed to be reached:

$$L + M \varsigma C \tag{1.26}$$

where C denotes the complex formed. Then the Gibbs energy is minimized for a solution prepared using n_1 moles of water:

$$G^{eq} = n_L^{eq} \cdot \mu_L^{eq} + n_M^{eq} \cdot \mu_M^{eq} + n_C^{eq} \cdot \mu_C^{eq} + n_1 \cdot \mu_1^{eq} \tag{1.27}$$

which completes the thermodynamics of titration calorimetry.

The composition of solutions is expressed in various ways, like *molar fractions*, x_j, for substance *j*, *molalities*, m_j, for solute *j*, *concentrations*, c_j, for substance *j*, or *amount of chemical substances*, n_j. By definition:

$$\mu_j = \mu_j\left(m_j = m^0\right) + R \cdot T \cdot \ln\left(\frac{m_j \cdot \gamma_j}{m^0}\right) \tag{1.28a}$$

where, at all T and p, $\lim_{m_j \to 0} \gamma_j = 1.0$. In ideal-dilute solution (no solute-solute interaction) the activity coefficient $\gamma_j = 1.0$ and $\mu_j\left(m_j = m^0\right) \equiv \mu_j^0$ is the reference chemical potential for solute *j* in an ideal solution where $m_j = 1\,\mathrm{mol} \cdot \mathrm{kg}^{-1}$. Then for an ideal solution:

$$\mu_j = \mu_j^0 + R \cdot T \cdot \ln\left(\frac{m_j}{m^0}\right) \tag{1.28b}$$

1.7.2 Thermodynamics of Complexation

One way to treat the thermodynamic data is a classification by the factors contributing to the complex stability, using the sign of changes in enthalpy, H and entropy, S. In terms of finite difference processes, all host-guest interactions fall into one of the following four categories, the first term being the major contributor [137];

$$\begin{aligned} &\Delta H < 0,\ \Delta S > 0 \\ &\Delta H < 0,\ \Delta S < 0 \\ &\Delta S > 0,\ \Delta H < 0 \\ &\Delta S > 0,\ \Delta H > 0 \end{aligned} \tag{1.29}$$

The host-guest complexes in the first two categories are stabilized primarily by the favorable enthalpy change, $\Delta H < 0$, which is either assisted by positive entropy change ($\Delta S > 0$) or cancelled in part by the negative entropy change ($\Delta S < 0$). Contrarily, in the last two categories, the major driving force to form the complex is the positive entropy change, $\Delta S > 0$, accompanied by minor stabilizing ($\Delta H < 0$) or destabilizing enthalpic contribution ($\Delta H > 0$).

The thermodynamic terms have also been correlated with each other in several chemical and biological molecular recognition systems [138]. As for instance, many authors reported in their studies on cation binding by crown ethers that ΔH and ΔS compensate each other, with ΔH being the dominant quantity in determining the complex stability. Similar compensatory $\Delta H - \Delta S$ effects we observed in various biological molecular recognition processes, yet case

studies were only reported [139] until recently [140], when validity and physical meanings of this compensation effect was treated in more detail.

For a mixture of chemical species i, $i = 2,3,...$, the affinity A [J/mol] has the expression [141]:

$$A \equiv -\sum_i \nu_i \mu_i \tag{1.32}$$

where μ_i is the chemical potential [J/mol] and ν_i is the stoichiometric coefficient of species i. The differential Gibbs energy of the mixture is given by eq. (1.19):

$$dG = V \cdot dp - S \cdot dT - A \cdot d\xi = V \cdot dp - S \cdot dT + \sum_i \nu_i \mu_i d\xi \tag{1.33}$$

Spontaneous chemical processes, at constant T and p, evolve towards thermodynamic equilibrium, while reactants and products coexist. From eq. (1.33) results:

$$\left(\frac{\partial G}{\partial \xi}\right)_{p,T} = -A = \sum_i \nu_i \mu_i \tag{1.34}$$

The chemical equilibrium is characterized by $A = 0$, which yields:

$$\sum_i \nu_i \mu_i = 0 \tag{1.35}$$

For a reaction $A \leftrightarrows B$ at equilibrium, their stoichiometric coefficients are $\nu_A = -1$ and $\nu_B = +1$, respectively, and their chemical potentials $\mu_A = \mu_B$. Turning eq. (1.33) into finite differences and substituting the values of the stoichiometric coefficients and chemical potentials, the free enthalpy change ΔG (J/mol) is obtained as:

$$\Delta G = \sum_i \nu_i \mu_i = \sum_i \nu_i \left(\mu_{0i} + RT \ln x_i f_i\right) = \Delta G^{\Theta} + RT \ln \prod_i \left(x_i f_i\right)^{\nu_i} \tag{1.36}$$

where:

ΔG^{Θ}	free standard enthalpy (T = 298.15 K, p = 1.013 bar), [J/mol]
R	gas constant (8.314 J/(K·mol))
T	absolute temperature [K]
x_i	molar fraction of component i
f_i	activity coefficient of component i

Since at chemical equilibrium the free enthalpy change $\Delta G \to 0$, the expression of free standard enthalpy is obtained from from eqs. (1.33) and (1.36):

$$\Delta G^{\Theta} = -RT \cdot \ln K_P \tag{1.37}$$

where K_P is the mass action constant.

The following equations can be written for a reversible complex formation at equilibrium:

$$\begin{aligned} M + L &\leftrightarrows ML \\ ML + L &\leftrightarrows ML_2 \\ &\partial \\ ML_{N-1} + L &\leftrightarrows ML_N \end{aligned} \tag{1.38}$$

The binding constant K_N of complex formation is defined by the following equation:

$$
\begin{aligned}
K_1 &= \frac{[ML]}{[M][L]} \\
K_2 &= \frac{[ML_2]}{[ML][L]} \\
&\vdots \\
K_N &= \frac{[ML_N]}{[ML_{N-1}][L]}
\end{aligned}
\tag{1.39}
$$

where: $[M]$, $[L]$, $[ML]$, and $\left[ML_N\right]$ are the equilibrium concentrations of metal ions, ligand and complex formation. N represents the maximum number of coordination [142]. The total binding constant β_N is the product of the individual binding constants of complexes formed:

$$
\beta_N = K_1 K_2 K_3 \ldots K_N = \frac{[ML_N]}{[M][L]^N} \tag{1.40}
$$

Taking into account the activity coefficients, f_i, of the species involved in reaction, the thermodynamic equilibrium constant K_N^{th} can be written as:

$$
K_N^{th} = K_N \cdot \frac{f_{ML_N}}{f_{ML_{N-1}} \cdot f_L} = K_N \cdot k_A \tag{1.41}
$$

where:

k_A	correction factors of activity coefficients
f_{ML_N}	activity coefficients of $\left[ML_N\right]$ species
$f_{ML_{N-1}}$	activity coefficients of $\left[ML_{N-1}\right]$
f_L	activity coefficient of ligand $[L]$

The expression of the activity coefficients are derived from the Debye-Hückel Theory [143]:

$$
\begin{aligned}
\log f_i &= -\frac{A z_i^2 \sqrt{I}}{1 + Ba\sqrt{I}} \\
A &= \sqrt{\frac{2\pi N_A}{1000}} \cdot \frac{e^3}{2.303\sqrt[3]{k\varepsilon T}} \\
B &= \sqrt{\frac{8\pi N_A e^2}{1000 k\varepsilon T}}
\end{aligned}
\tag{1.42}
$$

where:

z_i	charges of the cation or the anion
I	ionic strength
a	ion size (about 400 pm [143])
N_A	Avogadro constant (6.023×10^{23} mol^{-1})
k	Boltzmann constant (1.381×10^{-23} J/K)
e	elementary electrical load (1.602×10^{-19} C)
ε	dielectric constant of solvents
T	absolute temperature inK

The changes in standard enthalpy, ΔH^0, and standard entropy, ΔS^0, are related to the standard free enthalpy change:

$$\Delta G^{\Theta} = \Delta H^{\Theta} - T \cdot \Delta S^{\Theta} \tag{1.43}$$

with

ΔH^{Θ} at $T = 298.15$ K and $p = 1.013$ bar in J/mol

ΔS^{Θ} at $T = 298.15$ K and $p = 1.013$ bar in J/K·mol

The combination of eqs. (1.37) and (1.43) gives:

$$ln\, K_P = -\frac{\Delta H^{\Theta}}{RT} + \frac{T\Delta S^{\Theta}}{RT} \tag{1.44}$$

The solvation and associated desolvation process of metal cation, ligand, and formed complex are the contributions which participate at the complexation reaction.

- Desolvation of the cations, M^{n+}:

  $[M^{n+}]_{aq.} \varsigma [M^{n+}] + x \,/\, H_2O$

- Desolvation of the ligand, L:

  $[L]_{aq.} \varsigma [L] + y \,/\, H_2O$

- Complex formation between the desolvated ligand and the desolvated cation:

  $[M^{n+}]_{aq.} + [L] \varsigma [ML^{n+}]$

- Solvation of originated complexes ML^{n+}:

  $[ML^{n+}] + [L] \varsigma [ML^{n+}]_{aq.}$

The expression of the mass action constant, K_P, for the complex formation taking into account the solvation and desolvation processes can be put after regrouping in the form of a product of a constant, K, which comprises the interaction between the ligand and the cation, times a constant, K_{sol}, that contains the influences of the solvent:

$$K_P = \underbrace{\frac{[ML^{n+}]_{aq.}}{[M^{n+}]_{aq.} \cdot [L]_{aq.}}}_{K} \cdot \underbrace{\frac{[H_2O]^x \cdot [H_2O]^y}{[H_2O]^z}}_{K_{sol.}} = K \cdot K_{sol.} \tag{1.45}$$

where:

x number of solvent molecules of species $[M^{n+}]_{aq.}$

y number of solvent molecules of species $[L^{n+}]_{aq.}$

z number of solvent molecules of species $[ML^{n+}]_{aq.}$

The effect of solvation is generally difficult to cast in quantitative terms and, therefore, quite often neglected by taking $K_{sol} = 1$. Comparisons with data from literature are relevant if the constants are measured rigorously in the same solvent at identical temperature.

1.7.3 Methods for determination of equilibrium constants in solution

The equilibrium constant is used as a criterion for the evaluation of the host-guest complexation process. There are specific methods for determination of the equilibrium constant, *K*, for reactions in solution.

1.7.3.1 Calorimetry

Calorimetry has a huge impact on understanding the energetic aspects of chemical reactions. It gives detailed information about the thermodynamic background of the molecular recognition. Thus it becomes possible to separate the contributions for the complex formation into enthalpic (e.g., ion-ion interactions, ion-dipole interactions, etc.) and entropic factors (solvation effects, conformational changes, etc.).

Calorimetry is a sensitive and versatile technique that requires small sample sizes and nearly any solvent [144]. Extensive thermodynamic data obtained by calorimetric measurements of macrocyclic binding of ions have been reviewed by Izatt *et al.* [70, 71, 145]. The titration calorimetry is a technique where one reactant is titrated into another and the temperature of the system is measured as a function of added titrant [146]. In Figure 21 are presented two typical titration curves. The reaction of cucurbit[6]uril with L-valine is exothermic and the complexation of the dipeptide gly-val with α-cyclodextrin endothermic [147].

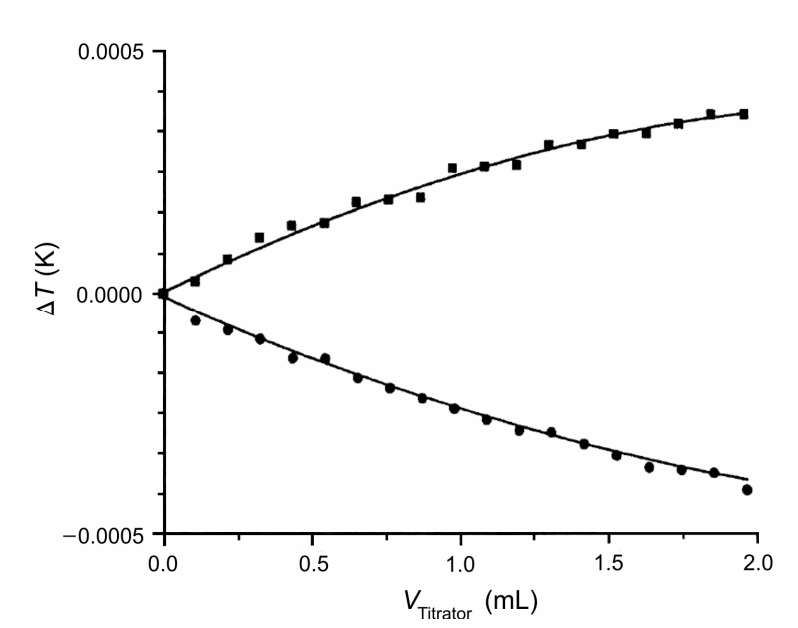


Figure 21: Temperature changes during the titration of cucurbit[6]uril with L-val (■) in aqueous formic acid (50%, v/v) and of α-cyclodextrin with gly-val (•) in aqueous solution at $T = 25^{o}$ C [147].

Izatt and his co-workers [148-151] established the calorimetric titration technique and used this technique to study the interactions between synthetic host and guest molecules. The titration curves obtained by calorimetric titrations allow the calculation of equilibrium constants to a given system and reaction enthalpies if the equilibrium constants are within certain limits [152]. By using competitive calorimetric titrations even larger equilibrium constants can be obtained [153].

The stability constants should be in the range of $10^2 - 10^4$ L/mol. The value of the reaction enthalpy, ΔH, should be as high as possible to increase the accuracy. Also, the solvent should be available in high purity without any problems [154].

To measure the stability constants and reaction enthalpies, solutions of ligands ($0.06 - 0.08$ mol/L) were added continuously to a guest solution ($2 - 5 \times 10^{-3}$ mol/L). The heat Q produced during titration is related to the reaction enthalpy, ΔH, and the number of moles of the complex formed, Δn. In its turn, Δn depends on the stability constant. In the present work, only the formation of 1:1 complexes is examined, for which the reaction heat Q for any time t of titration is given by:

$$Q_t = \Delta n_t \Delta \overline{H}^{\Theta} \tag{1.46}$$

where:

Q_t	heat produced at time t of titration (J)
Δn_t	number of moles of the complexes formed at time t (mol)
$\Delta \overline{H}^{\Theta}$	molar enthalpy change in reaction under standard conditions (J/mol)

It shows the general connection between the heat Q_t, the change in complex mole number Δn_t, and the change of reaction enthalpy $\Delta \overline{H}^{\Theta}$. Considering the complex reaction between metal cations M^{n+} and ligand L yielding ML^{n+}, the concentrations of metal cation, ligand, and complex at equilibrium can be written as:

$$c_M = \left[M^{n+} \right] + \left[ML^{n+} \right] \tag{1.47}$$

$$c_L = [L] + \left[ML^{n+} \right] \tag{1.48}$$

where:

$[ML^{n+}]$	equilibrium concentration of complex formation at time t of titration (mol/L)
$[M^{n+}]$	concentration of cations M^{n+} at time t of titration (mol/L)
$[L]$	concentration of ligand L at time t of titration (mol/L)
c_M	total concentration of cations M^{n+} at time t of titration (mol/L)
c_L	total concentration of ligand L at time t of titration (mol/L)

Invoking the equation of the mass action constant, K, under application of the activity corrections from eq. (1.42) one gets the thermodynamic equilibrium constant of the reaction:

$$K^{th} = \underbrace{\frac{[ML^{n+}]}{[M^{n+}][L]}}_{K} \cdot \underbrace{\frac{f_{ML^{n+}}}{f_{M^{n+}} \cdot f_L}}_{k_A} \tag{1.49}$$

Yet the concentration of the complex $\left[ML^{n+}\right]$ is given as a function of the equilibrium constant, K:

$$\left[ML^{n+}\right] = \frac{\left(c_M + c_L + \frac{1}{K}\right)}{2} \pm \sqrt{\frac{\left(c_M + c_L + \frac{1}{K}\right)^2}{4} - c_M c_L} \tag{1.50}$$

The concentrations above are all known, only the value of the equilibrium constant K is not. The concentration of the complex formed at any time t times the total volume, V (total volume of titrant + titrated), gives the change in mole number:

$$\Delta n_t = \left[ML^{n+}\right] \cdot V \tag{1.51}$$

The calculation of the values of the equilibrium constant K and the molar standard reaction enthalpy, $\Delta\overline{H}^{\Theta}$, is carried out by minimizing the quadratic function defined as follows:

$$U\left(K, \Delta\overline{H}^{\Theta}\right) = \underbrace{\min}_{K} \sum_{t=1}^{m} \left(Q_t - \Delta n_t \Delta\overline{H}^{\Theta}\right)^2 \tag{1.52}$$

where:

Q_t	heat exchanged during the experiment (J)
$\Delta n_t \Delta\overline{H}^{\Theta}$	number of moles of the complex formed times the molar standard enthalpy reaction (J).
m	number of data points (i.e., experiments) from the titration curve.

At minimum, the partial derivatives of the quadratic error function $U\left(K, \Delta\overline{H}^{\Theta}\right)$ equal 0:

$$\frac{\partial U\left(K, \Delta\overline{H}^{\Theta}\right)}{\partial \Delta\overline{H}^{\Theta}} = \sum_{t=1}^{m} Q_t \Delta n_t - \sum_{t=1}^{m} \Delta n_t^2 \Delta\overline{H}^{\Theta} = 0 \tag{1.53a}$$

$$\frac{\partial U\left(K, \Delta\overline{H}^{\Theta}\right)}{\partial K} = \sum_{t=1}^{m} \left(Q_t - \Delta n_t \Delta\overline{H}^{\Theta}\right) \cdot \frac{\partial \sum_{t=1}^{m} \Delta n_t \Delta\overline{H}^{\Theta}}{\partial K} = 0 \tag{1.53b}$$

Eq. (1.53a) gives the change of the molar standard enthalpy reaction:

$$\Delta\overline{H}^{\Theta} = \frac{\sum_{t=1}^{m} Q_t \Delta n_t}{\sum_{t=1}^{m} \Delta n_t^{\,2}} \tag{1.54}$$

In practice, the minimization of the error quadratic function $U\left(K, \Delta\overline{H}^{\Theta}\right)$ is performed by an iterative procedure on the equilibrium constant, K. The procedure starts by fixing a value for K, followed by calculating the concentrations of all the species involved in the complex reaction, namely $\left[ML^{n+}\right]$, $\left[M^{n+}\right]$, and $[L]$, which allows the calculation of the change in mole number, Δn_t, and, subsequently, the change in molar standard enthalpy reaction, $\Delta\overline{H}^{\Theta}$, using the measured heat, Q_t. The quadratic form (sum of square errors), $U\left(K, \Delta\overline{H}^{\Theta}\right)$, is built and minimized after the value of the constant K:

$$U\left(K, \Delta\overline{H}^{\Theta}\right) = \underbrace{\min}_{K} \sum_{t=1}^{m} \left(\underbrace{Q_t}_{\text{exp}} - \underbrace{\Delta n_t \Delta\overline{H}^{\Theta}}_{calculated} \right)^2 \tag{1.55}$$

The graphical representation in semi logarithmic axes of $U\left(K, \Delta\overline{H}^{\Theta}\right)$ as function of the assumed stability constants, K, parabolically tends to the ideal case, which goes through a

minimum. The value of K corresponding to this minimum is the stability constant for the chemical equilibrium of the complex.

1.7.3.2 Total Organic Carbon (TOC)

The TOC value is related to the ligand concentration $[L]_{sat}$ in solution:

$$TOC_0 = f_1[L]_{sat} \tag{1. 56}$$

where f_1 is the proportionality factor. For a complex formed between nearly insoluble ligand with cation the following equation can be written by using eqs. (1.48 and 1.56):

$$TOC = \underbrace{f_1[L]_{sat}}_{TOC_0} + f_2[LM^{n+}] \tag{1.57}$$

By applying eqs. (1.47 and 1.48) and the expression of the mass action constant from eq. (1.45) one gets:

$$\frac{TOC}{TOC_0} - 1 = \underbrace{\frac{f_2}{f_1}\frac{K}{1+K[L]_{sat}}}_{b} c_M \tag{1.58}$$

Plotting $\left(\frac{TOC}{TOC_0} - 1\right)$ as a function of the total salt concentration c_M one expects a straight line with a slope b. From this slope, the stability constant of the complex formed can be calculated using eq. (1.59):

$$K = \frac{b}{\left(\frac{f_2}{f_1}\right) - b \cdot [L]_{sat}} \tag{1.59}$$

The proportionality factors f_1 and f_2 are identical for the pure ligand and the complex so that the equation (1.59) can be written as follows:

$$K = \frac{b}{1 - b \cdot [L]_{sat}} \tag{1.60}$$

If the solubility of the ligand is low, then the term $b[L]_{sat} << 1$, which equates to the identity between the slope b and the stability constant K [155, 156].

1.7.3.3 UV-Visible Spectrophotometry

The formation of complexes in solution can be investigated by means of several experimental methods. The most common experimental techniques used for evaluation of the equilibrium constants are potentiometry, conductometry, polarography, NMR, calorimetry, UV-Vis and fluorescence spectroscopy, mass spectrometry, electrophoresis, and kinetic measurements [25, 157-160].

The equilibrium constant can be calculated from the concentration dependence of any property proportional to the concentration of one of the components. The property (X) can be the absorbance, the fluorescence, the position of a NMR signal, the reaction rate, the

conductance, etc. The proportionality between X and the concentration of a given species L is expressed as follows:

$$X = x_L[L] \tag{1.61}$$

where: x_L is an intrinsic molar property of L, such as the molar absorptivity ε, the rate constant k, etc. The observed value of X is considered to be the sum of contributions from all components. As for instance, in the case when the observed X value (X_{obs}) is due to the contribution of only one complexation partner L in free and complexed forms; as long as $x_M = 0$, the following dependence holds:

$$X_{obs} = x_L[L] + x_{LM}[LM] \tag{1.62}$$

The ultraviolet and visible spectrophotometry [161-167] works in a spectral range corresponding to electronic transitions which are observed for different compounds. Processing of spectrophotometric data relies on the Beer-Lambert-Bouguer law, which is commonly known as the Beer's law for short:

$$A = \varepsilon \cdot l \cdot [L] \tag{1.63}$$

where:

ε	the molar absorptivity ($M^{-1}cm^{-1}$)
l	the optical pathlength (cm)
$[L]$	concentration of L (mol/L)

The linearity between A and $[L]$ depends on the instrument employed and is restricted by the effect of stray light [25, 168, 169]. In this respect, the precision in A reaches its maximum at intermediate values of A, somewhere around 0.4. There are some deviations from the Beer-Lambert-Bouguer law, such as lack of monochromasy of the incident radiation, effect of some instrumental factors, medium or intermolecular effects, changes in chemical equilibria, dissociation of the absorbing complex, and effect of fluorescence [170]. Absorption spectra in the UV-Vis regions correspond with plots of the absorbed radiation against the wavelength, λ, wavenumber, $\bar{\nu}$, or frequency, ν. The electronic transitions are characterized by absorption peaks usually of Gaussian character which provide qualitative evidence of the analyte species, its stoichiometry and structure or of chemical equilibria in solutions.

Considering eq. (1.38) for a reversible complex formation at equilibrium:

$$\begin{aligned} M + L &\varsigma ML \\ ML + L &\varsigma ML_2 \\ &\partial \\ ML_{N-1} + L &\varsigma ML_N \end{aligned} \tag{1.38}$$

with equilibrium constants presented in eq. (1.39)

$$K_1 = \frac{[ML]}{[M][L]}$$
$$K_2 = \frac{[ML_2]}{[ML][L]} \qquad (1.39)$$
$$\vdots$$
$$K_N = \frac{[ML_N]}{[ML_{N-1}][L]}$$

where: [*M*], [*L*], [*ML*] and [ML_N] are the equilibrium concentrations of metal ions, ligand and complex formation, and *N* represents the maximum number of coordination. For *N = 1* in the case of 1:1 host-guest complexation between species *L* and *M*, the expression of equilibrium constant is given by:

$$K = \frac{[ML]}{[L][M]} \qquad (1.64)$$

The most common procedure for determination of the equilibrium constants assumes measurements at variable concentration of one component and at fixed concentration of the other one. The mass balance for the total concentrations of components is given below:

$$[c_L] = [L] + [ML] \qquad (1.65)$$

$$[c_M] = [M] + [ML] \qquad (1.66)$$

where:

c_M total concentration of species *M* (mol/L)

c_L total concentration of species *L* (mol/L)

In this case, it is sufficient to determine the equilibrium concentration of only one component *L*, *M*, or *LM*, because the other two can be calculated from the mass balance equations [1.65-1.66] [25].

Significant influences on ε and plots of absorbance versus analyte concentration are observed when dissociation, association or polymerization of absorbing species, shifts in equilibria between tautomers or modification solvation of absorbing species take place. These interactions are dependent on the reaction conditions and the concentration of the absorbing species involved in the experiment [170].

The equations relating the concentrations and absorbencies of each species involved in determination of binding constants of a complex formation between host and guest species investigated by means of UV-visible spectrophotometry are presented below. Starting from the expression of absorbance given in equation (1.63) for 1:1 host guest complexation between species *M* and *L*, the absorbance *A* of the solution at a constant wavelength is given by following equation:

$$A = l\varepsilon_L[L] + l\varepsilon_{ML}[ML] \qquad (1.67)$$

where:

ε_L molar absorptivity of the ligand *L* ($M^{-1}cm^{-1}$)

ε_{ML} molar absorptivity of the complex *ML* ($M^{-1}cm^{-1}$)

l optical pathlength (cm)

The mass balance for the total concentrations of species, c_L and c_M, is represented above in eqs. (1.65) and (1.66), where [L], [M], and [ML] are the concentrations of the ligand, metal cation, and complex, respectively, at equilibrium.

The expression of [L] can be put in the form:

$$[L] = \frac{\sqrt{(1+[c_M - c_L]K)^2 + 4Kc_L} - [1+(c_M - c_L)K]}{2K} \tag{1.68}$$

For simplification, new mathematical expressions are introduced:

$$r = (c_M - c_L)K + 1 \tag{1.69}$$

and

$$D = r^2 + 4Kc_L \tag{1.70}$$

so that eq.(1.68) can be rewritten alternatively as:

$$[L] = \frac{\sqrt{r^2 + 4Kc_L} - r}{2K} = \frac{\sqrt{D} - r}{2K} \tag{1.71}$$

Further on, [ML] can be expressed as a function of [L]:

$$[ML] = c_M \frac{K[L]}{1+K[L]} \tag{1.72}$$

and $[M]$ is given by:

$$[M] = \frac{c_M}{1+K[L]} \tag{1.73}$$

The above complexation model was used to fit the data from spectrophotometric method and to determine the binding constants of the complex formed.

2 The Aim

The ability of the macrocyclic ligands to bind by noncovalent interactions, to extract, and to allow transport of charged or uncharged substrates through membranes is a current issue in chemistry and particularly, in supramolecular chemistry. In recent years, understanding the process of ion extraction and transport from an aqueous phase to an organic phase has been a challenging issue in solution and complexation chemistry. The study of the complex formation between different ligands such as crown ethers, crown ether derivatives, and [2.2.2] cryptand, and alkali metal cations and ammonium ion as guests in nonpolar solvents (chloroform, dichloromethane, 1,2-dichloroethane, and carbon tetrachloride) is presented aimed at emphasizing the importance of the reaction medium for the complex formation. The research along this line is envisaged to provide a deeper understanding of the nature of interaction concerning charged species involved in the complexes studied.

The development of synthetic ion channel models involving crown ethers, which selectively transport cations and small molecular species through membranes, has lead to an increasing importance of studies on the influence of the environment over the crown ether complexes with cations. Moreover, during the extraction process, water molecules are coextracted with the metal ions, metal complexes, and anions into the water-saturated organic solvent used. As a result, the concentration of water in the organic phase is not constant. Up to date, there is little knowledge of the influence of water molecules on the complex stability. In this respect, the studies concerning hydration of the crown ether molecules and their complexes with cations in nonpolar solvents are of special interest in relation with processes like solvent extraction and the transport through liquid membranes. Therefore, the influence of polar solvents like water, methanol, acetone, and acetonitrile on the complex formation of crown ethers and [2.2.2] cryptand with Na^+, K^+, Rb^+, and Cs^+ dibenzyldithiocarbamate salts and ammonium salts in halogenated organic solvents, chloroform, dichloromethane, 1,2-dichloroethane and carbon tetrachloride is investigated in the present work. This way, the interactions between crown ethers and water molecules in chloroform are investigated.

Studies of the complex formation between two crown ether derivatives (an aza-15-crown-5 derivative and a benzo-15-crown-5 derivative) and alkali metal cations: Li^+, Na^+, K^+, Rb^+, and Cs^+ as dibenzyldithiocarbamate salts in chloroform by means of spectrophotometric measurements are performed. The complex formation of α-cyclodextrin with uncharged guests such as amides and nitriles, respectively, in aqueous solution is investigated in order to highlight the nature of the interactions concerning uncharged species involved in these complexes.

3 Complex Formation of Crown Ethers and Cryptands with Cations in Nonpolar Medium

3.1 Introduction

Crown ethers exhibit an extremely large ability to form complexes with alkali metal cations and neutral or ionic organic species [1, 16, 39]. They bind the majority of elements of the periodic table. The chemistry of crown ethers (Figure 1.12) starting with Pedersen in 1967 [16, 17] has been enhanced by several interdisciplinary contributions [171]. The significant factors involved in solution selectivity of the crown ethers towards different guests as previously mentioned in section 1.4 are the preorganisation and complementarity [172], the flexibility of both host and guest, the multiple interaction site, the solvation, and the chelate ring size [173]. The flexibility of crown ethers entails some very interesting properties like solubility in both aqueous and lipophilic solvents and fast, reversible ion binding characteristics [174]. Thus, 18C6 exhibits a perfect balance between hydrophilicity and lipophilicity because it allows exposing either the hydrophilic ether oxygen atoms or the lipophilic ethylenic groups to the surrounding medium. Hence, the attractive applications as ionophore in phase transport catalysis or in sensing and signaling applications [175].

Because the complexation usually takes place in solution for stabilization of crown ether complexes, an additional factor of solvation has to be considered. As it is well known, the thermodynamic stability of a complex depends on the nature of the solvent, mainly because the solvation of all reactants in the system competes with the interactions between ligands and its complex partners. The complexation behavior of crown ethers in less polar or even nonpolar organic solvents depends on the existence of ion pairs [144]. So, in other words, depending on the nature of the solvent, complex formation may be strongly affected by solvation of the reactants.

3.2 Influence of solvent composition on the complex formation of 18C6 with cations

In order to get more information about the influence of the solvent polarity, the reaction of 18-crown-6 with ammonium perchlorate is studied in different mixtures of water with dioxane. By using mixtures of water-dioxane, it is possible to study the complex formation behavior of 18C6 with cations on a large range of dielectric constant value of the reaction medium. In pure water, the results of the complex formation are in accordance with previously published results [97].

The dependence of the stability constants and reaction enthalpies for the complex formation of 18C6 with ammonium perchlorate in a mixture of water and dioxane at various proportions is specified in Figure 22. With the increase of dioxane concentration, the values of the stability constants and reaction enthalpies increase as well.

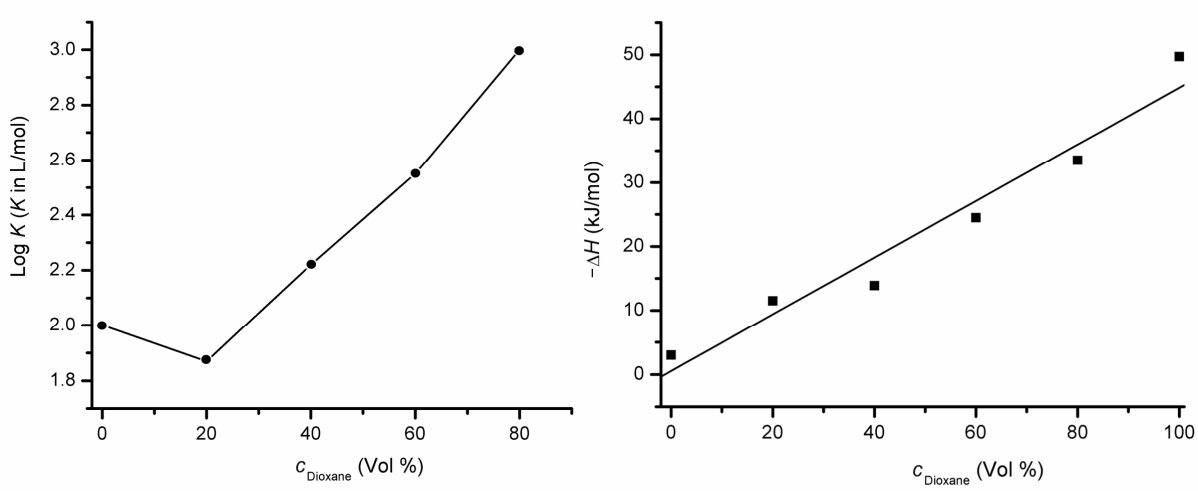


Figure 22: Dependence of the logarithmized stability constant log K (●) and the reaction enthalpy ΔH (■) on the concentration of dioxane in water for the reaction of 18C6 with ammonium perchlorate.

As expected, the enthalpy values, ΔH , for the reaction between 18C6 and ammonium perchlorate in a mixture of dioxan in water, monotonically decrease with the increase in the dielectric constant (Figure 23).

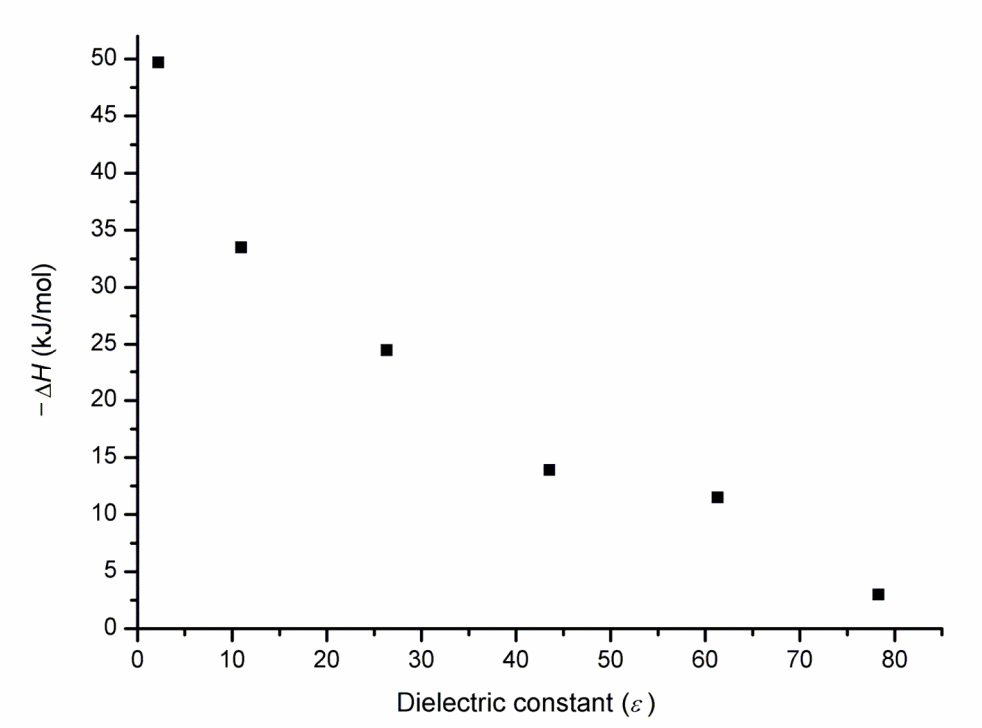


Figure 23: Dependence of the reaction enthalpy ΔH for 18C6 with ammonium perchlorate in a mixture of dioxane in water as a function of the dielectric constant, ε.

The stability constants and thermodynamic values for complex formation between 18C6 and barium perchlorate, $Ba(ClO_4)_2$, in a mixture of dioxane in water obtained by calorimetric titrations are summarized in Table 1. It was reported that the reaction enthalpy for the complexation of Ba^{2+} by 18C6 in aqueous solution is not influenced by the different anions [154]. Instead they are able to change the values of the reaction entropy for the above complexation within certain limits.

Table 1: Logarithmized stability constants log K (K in L/mol) and ΔH (kJ/mol) and $T\Delta S$ (kJ/mol) for the complex formation of 18C6 with barium perchlorate in aqueous solution with different amounts of dioxane (vol %) at $T = 298.15$ K.

Dioxane	Log K	$-\Delta H$	$T\Delta S$
0	3.51[a]	31.5[a]	– 11.6[a]
20	3.94 ± 0.3	32.1 ± 0.8	– 9.7
50	4.56 ± 0.1	37.8 ± 0.5	– 11.9
60	4.71 ± 0.2	39.6 ± 0.6	– 12.8
70	4.99 ± 0.5	41.6 ± 1.1	– 13.2
80	> 5	40.5 ± 0.9	–

[a] From Ref. [154].

The data presented in Table 1 indicate that the values of stability constants and reaction enthalpies for complex formation of 18C6 with barium perchlorate in aqueous solution with different amounts of dioxane increase with the increase of dioxane concentration in water. The behavior in this case is quite similar with the complexation of ammonium perchlorate by 18C6. The variability of the reaction entropies is not significant over the full range of dioxane concentration.

In Figure 24 is given the dependence of the reaction enthalpy, ΔH, on the concentration of dioxane in water for the complex formation of 18C6 with ammonium perchlorate and the complex formation of 18C6 with barium perchlorate (see Section 7.4.1).

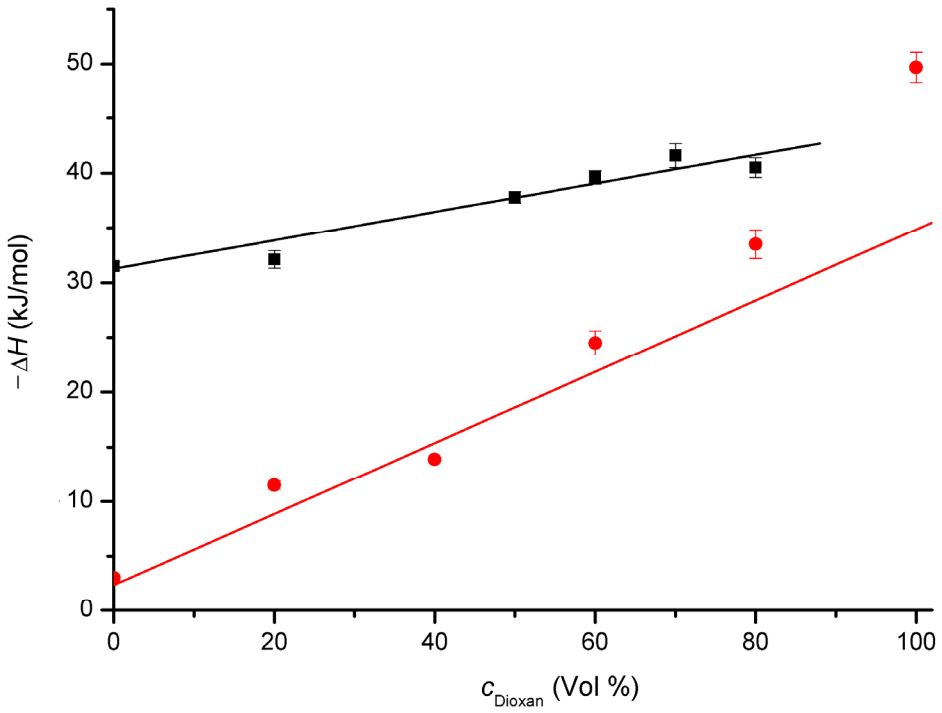


Figure 24: Dependence of the reaction enthalpy ΔH on the concentration of dioxane in water for the reaction of 18C6 with NH_4ClO_4 (●) and the reaction of 18C6 with $Ba(ClO_4)_2$ (■).

The plots in Figure 24 for the reaction enthalpy of barium and ammonium, respectively, are different due to the nature of the complexation interactions between 18C6 and ammonium (Figure 13) in comparison with 18C6 and barium. In case of the ammonium ion not only electrostatic interactions take place but also hydrogen bonds are formed between the ammonium ion and the donor atoms of the ligands. In this case the values of the reaction enthalpies are not comparable with those for the alkali ions.

3.3 Complexes of crown ethers with alkali metal cations in chloroform

Crown ethers interact strongly with alkali metal cations by charge-dipole interactions (Figure 10). The stability of the host-guest complexes of crown ethers with cations depends on structural factors such as the cavity size of the crown ether and the number, type, and position of the heteroatoms involved in the ring [98]. In this respect it is recognized the ability of 18C6 to form complexes with alkali metal ions in its cavity through unidirectional Coulombic forces ("spherical recognition") and to transport them into lipophilic phases [176]. Moreover, it was demonstrated that the solvation of the crown ether significantly affects the conformational state of the ring [98].

The complex formation of macrocyclic ligands with various cations and anions is strongly influenced by the solvent nature. Thus, the solvent characteristics, which include properties such as the level of structure, polarity, hydrogen bond donor/acceptor ability, polarizability, acidity/basicity, and hydrophobicity/hydrophilicity or other empirical parameters, mainly affect the interaction strength between the compounds [177-182].

In this Section the investigations on complex formation of crown ethers with alkali metal cations as dibenzyldithiocarbamate salts have been carried out in chloroform as nonpolar solvent in view of collecting more information about the nature of interactions involved in complexation. Thus, the complexation of Na^+, K^+, Rb^+, and Cs^+ by 12-crown-4, benzo-12-crown-4, 15-crown-5, benzo-15-crown-5, dibenzo-15-crown-5, and 18-crown-6 (Figure 12, section 1.4) in chloroform has been studied. Because of solubility in chloroform, the dibenzyldithiocarbamate salts of alkali metal and ammonium ions have been synthesized and used throughout all the calorimetric titrations [183] (see Section 7.2.1). The ionic radii of the alkali metal and ammonium cations along with approximate diameter of complementary crown ethers are summarized in Table 2.

Table 2: The ionic radii of alkali metals and ammonium, as well as the cavity size of the crown ethers and cryptand [2.2.2].

Cation	***Radius*** (Å)[a]	***Ligand***	***Cavity size*** (Å)[b]
Li^+	0.76	12-crown-6	0.60 – 0.75
Na^+	1.02	15-crown-5	0.86 – 0.92
K^+	1.38	18-crown-6	1.34 – 1.55
Rb^+	1.52	21-crown-7	1.70 – 2.10
Cs^+	1.67	Cryptand [2.2.2]	1.42
NH_4^+	1.40		
Ba^{2+}	1.42		

[a] From Ref. [184].
[b] From Ref. [98].

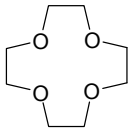
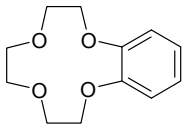
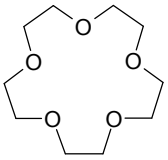
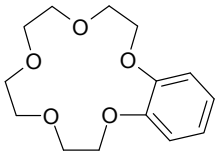
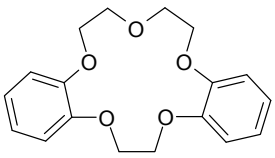
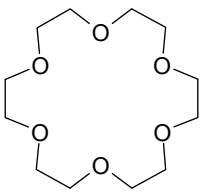
The values of the stability constants, log *K*, the reaction enthalpies, ΔH , and the reaction entropies, ΔS , for the complexation of crown ethers with alkali metal cations as dibenzyldithiocarbamate salts in chloroform obtained by calorimetric titrations are summarized in Table 3 (see Section 7.4.2). These results show that the values of stability constants for alkali metal cations as dibenzyldithiocarbamate salts with crown ethers are fairly high. The experimental results presented here indicate that the complexation is favored by the enthalpic contributions.

The values of stability constants for complex formation of crown ether 12C4 with alkali metal cations increase following the sequence: $K^+ < Rb^+ < Na^+ < Cs^+$. The same type of monotonical behavior is exhibited by the ligand B12C4, namely, $K^+ < Rb^+ < Na^+$. The increase of the values of the stability constants for the complex formation between 15C5 with alkali cations is the following: $Rb^+ < K^+ < Cs^+$, and for the complex of the ligand B15C5 with alkali cations under study, it is as follows: $Rb^+ < Cs^+ < K^+$. The same increase is observed in the case of the ligand DB15C5 complexes with alkali cations such as: $Rb^+ < Cs^+ < K^+$. In case of the reactions of the alkali metal cations with 18C6 no stability constants can be calculated from the calorimetric titrations. Therefore, the stability constants of all complexes formed are higher than 10^5 (L/mol).

As it was mentioned in Section 1.3, the size and shape complementarity of the alkali metal cations as guest with crown ethers acting as host are of particular importance concerning the selective stabilization or selective destabilization of complexes (Figure 10) [38, 39, 186].

The stability constants for complexes between 15C5, B15C5, and DB15C5 with Na^+ could not be calculated from the calorimetric titrations. Likewise the stability constants were not possible to be calculated from thermograms in the case of 18C6 complexes with alkali metal cations since their values are log K > 5. With the exception of the reaction between 18C6 and K^+, the values of stability constants for 12C4, B124, 15C5, B15C5, and DB15C5 with K^+ were found to be in the range log K = 3.10 (K^+-B12C4) to logK = 4.51 (K^+-B15C5).

Table 3: Logarithmized stability constants log K (K in L/mol), ΔH (kJ/mol), and $T\Delta S$ (kJ/mol), for the complex formation of alkali metal cations as dibenzyldithiocarbamate salts with different crown ethers in chloroform at $T = 298.15$ K.

Ligand	***Cation***	Log K	$-\Delta H$	$T\Delta S$
 12-Crown-4	Na^+	3.97 ± 0.1	38.1 ± 0.2	– 15.5 ± 0.6
	K^+	3.52 ± 0.1	29.2 ± 0.1	– 9.2 ± 0.5
	Rb^+	3.56 ± 0.1	17.2 ± 0.3	3.1 ± 1.5
	Cs^+	4.23 ± 0.3	3.7 ± 0.1	20.1 ± 1.2
 Benzo-12-crown-4	Na^+	4.15 ± 0.1	35.1 ± 0.7	– 11.5 ± 1.1
	K^+	3.10 ± 0.1	28.2 ± 0.7	– 10.5 ± 1.4
	Rb^+	3.70 ± 0.2	11.4 ± 0.6	9.7 ± 1.2
	Cs^+	-	< 1	-
 15-Crown-5	Na^+	-	52.3 ± 0.8	-
	K^+	3.66 ± 0.1	43.4 ± 0.1	– 22.0 ± 0.7
	Rb^+	3.64 ± 0.1	40.0 ± 1.4	– 19.3 ± 1.8
	Cs^+	3.89 ± 0.2	31.0 ± 1.5	– 8.9 ± 0.4
 Benzo-15-crown-5	Na^+	> 5	50.3 ± 0.4	-
	K^+	4.51 ± 0.1	40.2 ± 1.2	– 14.6 ± 2.0
	Rb^+	4.08 ± 0.1	36.8 ± 0.8	– 13.9 ± 1.0
	Cs^+	4.35 ± 0.2	26.5 ± 1.0	– 1.8 ± 1.1
 Dibenzo-15-crown-5	Na^+	> 5	38.2 ± 0.6	-
	K^+	4.05 ± 0.2	34.7 ± 1.2	– 11.7 ± 2.1
	Rb^+	3.85 ± 0.1	30.7 ± 1.5	– 8.2 ± 2.2
	Cs^+	3.88 ± 0.1	20.2 ± 0.6	1.9 ± 0.7
 18-Crown-6	Na^+	> 5	45.4 ± 0.5 45.9 ± 0.3[a]	-
	K^+	> 5	70.2 ± 0.4 70.9 ± 0.2[a]	-
	Rb^+	> 5	66.5 ± 0.3 66.9 ± 0.1[a]	-
	Cs^+	> 5	57.6 ± 0.7 58.0 ± 0.5[a]	-

" – " intractable from thermograms.
[a] From Ref. [185].

The crown ether 12C4 ($r = 0.6$ Å) [184] and the ligands 15C5, B15C5, and DB15C5 ($r = 0.9$ Å) [184] are too small to accommodate the potassium ion ($r = 1.38$ Å) [184]. In this respect, the formation of 2:1 complexes of these crown ethers with K^+ in acetonitrile and propylene carbonate by means of potentiometric and calorimetric titrations have been reported [187].

The relationship between complex stability constants and the ionic radii of alkali metal ions for the complex formation between crown ethers and Na^+, K^+, Rb^+, and Cs^+ asdibenzyldithiocarbamates in chloroform by calorimetric titrations are given in Figure 25.

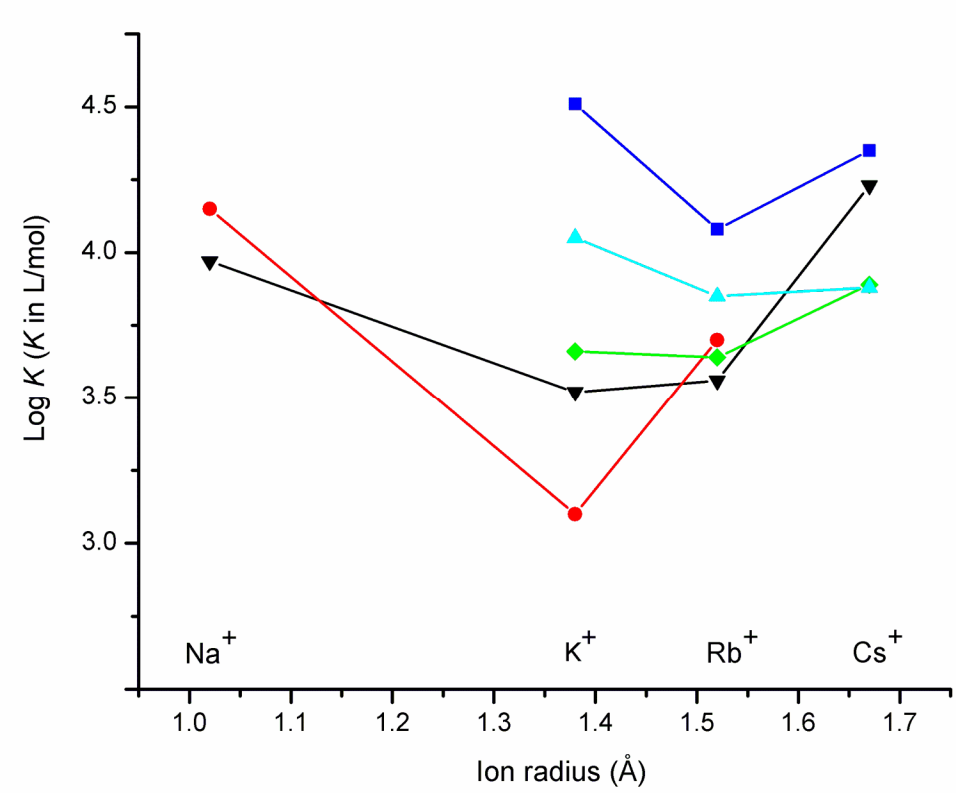


Figure 25: Dependence of the stability constant Log *K* of the complex formed between crown ethers: 12C4 (—▼—), B12C4 (—●—), 15C5 (—◆—), B15C6 (—■—), DB15C5 (—▲—), and alkali metal cations as dibenzyldithiocarbamate salts in chloroform as a function of the cation radius: [184].

The variation of log *K* values displayed in Figure 25 illustrates the variation from reaction enthalpy and reaction entropy for complex formation between crown ethers and alkali metal cations as dibenzyldithiocarbamate salts in chloroform. Moreover, the data displayed in Figure 25 suggest a preference of crown ethers, namely, 12C4 to bind Na^+ and Cs^+, and B12C4 to bind Na^+ and Rb^+ in chloroform.

The relationship between ΔH of complexation of Na^+, K^+, Rb^+, and Cs^+ (introduced as dibenzyldithiocarbamate salts) by these crown ethers and the cation radius is presented in Figure 26.

As normally expected, the data in Figure 26 indicate a decreasing monotonicity of the dependence of the reaction enthalpy on the cation radius for the complex formation between crown ethers and alkali metal cations in chloroform. That means, the reaction enthalpy ΔH decreases with the increase in the cation radius.

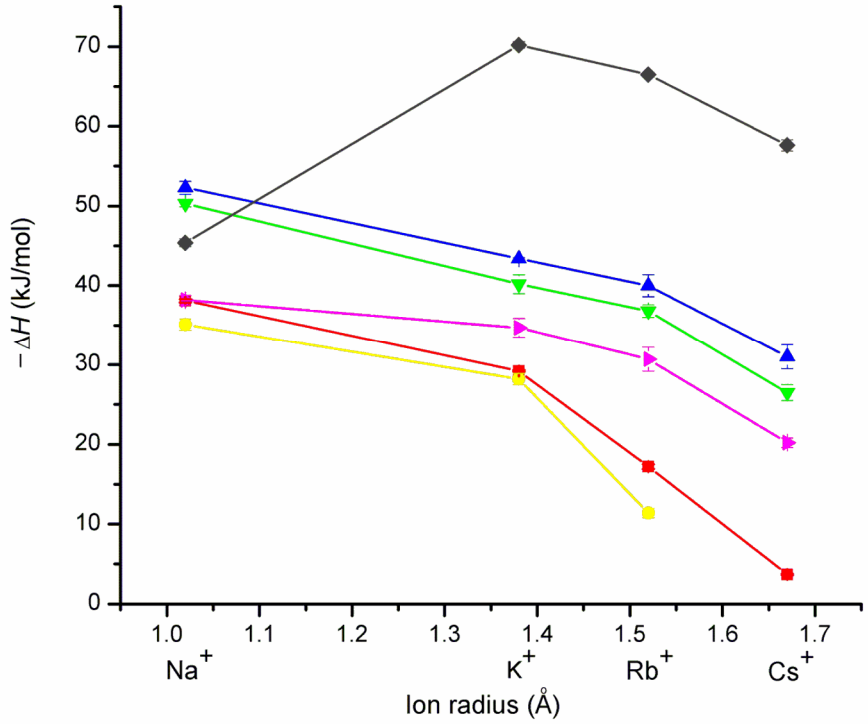


Figure 26: Relationship between the reaction enthalpy ΔH of the complex formed between crown ethers and alkali metal cations as dibenzyldithiocarbamate salts in chloroform and the cation radius: 12C4 (–■–), B12C4 (–●–), 15C5 (–▲–), B15C5 (–▼–), DB15C5 (–►–), 18C6 (–◆–) [184].

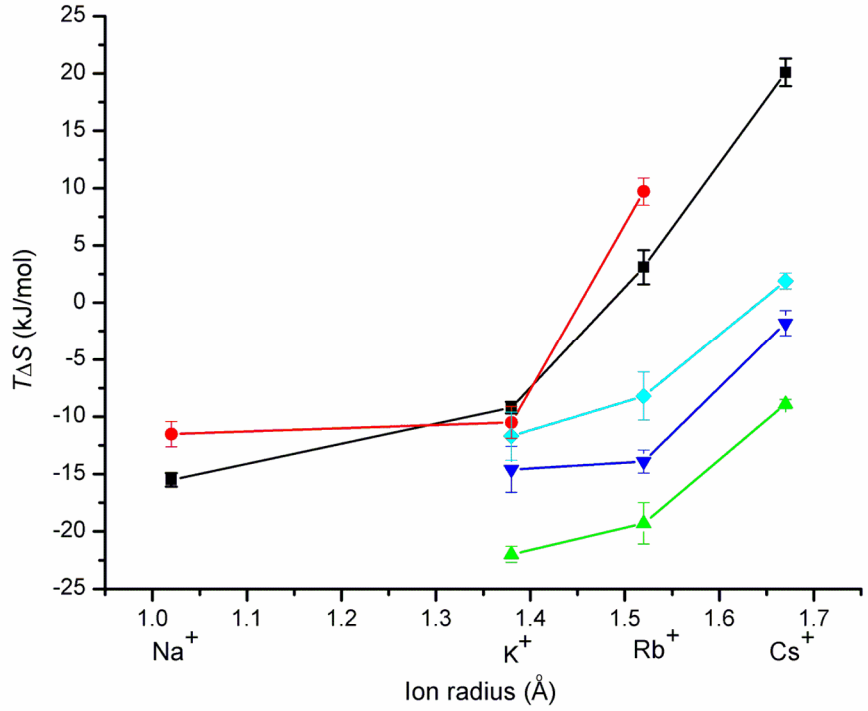


Figure 27: Relationship between the reaction entropy ΔS of the complex formation between crown ethers: 12C4 (–■–), B12C4 (–●–), 15C5 (–▲–), B15C5 (–▼–), DB15C5 (–♦–), and alkali metal cations as dibenzyldithiocarbamate salts in chloroform and the cation radius [184].

The ion-dipole interactions are responsible for complexation behavior of crown ethers towards alkali metal cations. With the increase of cation radius, the values of the reaction enthalpies decrease. Also, the fusion of benzo groups to the ligand (e.g., B12C4, B15C5, DB15C5) leads to a decrease of reaction enthalpies. Thus, the values of complexation enthalpies between B12C4 and B15C5 and DB15C5, respectively, and alkali metal cations (as dibenzyldithiocarbamate salts) are even lower than those for 12C4 and 15C5, respectively. The explanation is given by the ligand rigidity that rises by successive fusion with benzo groups, which gradually decreases the ligand flexibility. Likewise the basicity of donor oxygen atoms decreases when attached to the benzo group. As a result, the strength of the interaction is reduced.

The data also reveal the best fit of K^+ and 18C6 rather than all other alkali metal cations with 18C6 in terms of geometrical complementarity.

The relationship between reaction entropy, ΔS, of the complexation of crown ethers, 12C4, B12C4, 15C5, B15C5, and DB15C5 with Na^+, K^+, Rb^+, and Cs^+ as dibenzyldithiocarbamate salts in chloroform and the cation radius is presented in Figure 27. It came out that the values of the reaction entropy were in the range $T\Delta S = -22.0$ (for K^+-15C5) in kJ/mol to $T\Delta S = 20.1$ (for Cs^+-12C4). That is, the reaction entropy under the experimental conditions depends on the ligand nature only.

Further, the values of the reaction entropies decrease when a benzo group is attached to the ligand (e.g., B12C4 and B15C5 in Figure 27). When a second benzo group is added, the value of the reaction entropy continues to decrease by about the same amount (e.g., DB15C5 in Figure 27). The explanation is similar to the one given in the case of the reaction enthalpy presented above.

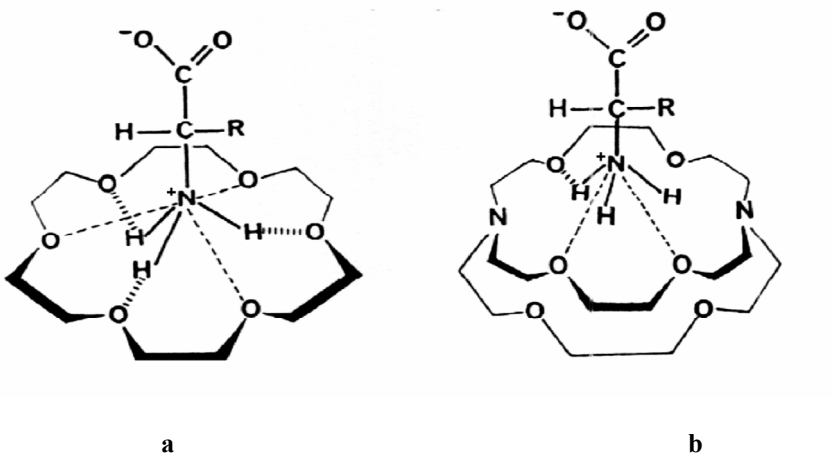
3.4 Reaction enthalpies of crown ethers and [2.2.2] cryptand complexation of ammonium ion in chloroform

In biological molecular recognition, the study of substituted ammonium compounds by receptor molecules is an essential issue for understanding the interactions between biological molecules and their applications in separation science [1]. The possibility of crown ethers to interact with the biologically interesting ammonium and substituted ammonium ions through hydrogen bonds was extensively investigated [97, 188-192]. As it was mentioned in Section 1.3, the NH_4^+ ion differs from alkali metals by the presence of directionality. This feature confers a particularity to the studies focused on ammonium ion complexation.

Electrostatic interactions between the nitrogen atom (positively charged) of the ammonium group and the oxygen donor atoms (negatively charged) of the crown ethers also contribute to the stabilization of these complexes. Three $N-H\cdots O$ hydrogen bonds are formed to alternating oxygen atoms of 18-crown-6 in the primary ammonium ion complexation (Figure 28a). The structure of ammonium ion complexes with crown ethers like 18C6 was observed in solution [77], in solid phase [76, 193], and in gas phase [74]. The crystal structures of the ammonium cation complexes suggest that the complementarity between NH_4^+ ($r = 1.48$ Å) and 18C6 ($r = 1.4$ Å) is perfect [194].

The complex of cryptand [2.2.2] with the primary ammonium ion is presented in Figure 28b [1]. In this case, only one $N-H\cdots O$ hydrogen bond is formed to one of the oxygen atoms of the cryptand [2.2.2] macroring [1].

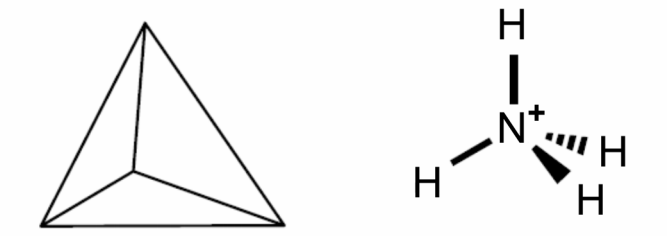
According to the data presented in literature, cryptands form stronger complexes with cations than crown ethers may form. This aspect is due to a greater encapsulation of the cation by the donor group chains [39].



a **b**

Figure 28: Ammonium complex formation with 18-crown-6 (**a**) and cryptand [2.2.2] (**b**) [1].

One characteristic of the ammonium ion is given by its tetrahedral charge distribution in contrast to all other cations with a spherical charge distribution [195] (Figure 29). Computational studies concerning the ammonium complexes with 18-crown-6 have also been reported [196, 197].



Tetrahedron structure Ammonium ion

Figure 29: Ammonium ion structure.

In this study, the reaction enthalpies of complex formation between ammonium salts such as ammonium dibenzyldithiocarbamate, $(C_6H_5CH_2)_2NC(S)S^-NH_4^+$, ammonium 1-pyrrolidinedithiocarboxylate, $C_4H_8NC(S)S^-NH_4^+$, and ammonium diethyldithiocarbamate, $(C_2H_5)_2NC(S)S^-NH_4^+$, with 18-crown-6, benzo 18-crown-6, dibenzo 18-crown-6, and [2.2.2] cryptand in chloroform by calorimetric titration have been investigated (see Section 7.4.3).

The values of the reaction enthalpies for the complexation of [2.2.2], 18C6, B18C6, and DB18C6 with ammonium salts in chloroform at $T = 298.15\,K$ are summarized in Table 4. The

values of the reaction enthalpies for the ligand [2.2.2] are higher compared to the corresponding values of the other ligands involved in experiments like 18C6, B18C6, and DB18C6. This is due to the number of donor atoms of the ligand [2.2.2], which is higher than that of the crown ethers under study.

Table 4: The reaction enthalpy ΔH (kJ/mol) for complex formation of ammonium salts with macrocyclic ligands and [2.2.2] cryptand in chloroform at $T = 298.15$ K.

Ligand	$-\Delta H$		
	$C_4H_8NC(S)S^-NH_4^+$	$(C_6H_5CH_2)_2NC(S)S^-NH_4^+$	$(C_2H_5)_2NC(S)S^-NH_4^+$
[2.2.2]	163.8 ± 5.2	135.9 ± 1.0	96.6 ± 2.2
18C6	117.6 ± 3.4	100.5 ± 1.8	29.5 ± 1.4
B18C6	85.4 ± 8.5	83.2 ± 5.1	5.6 ± 1.8
DB18C6	58.3 ± 9.8	78.0 ± 11.0	2.1 ± 1.2

From the data displayed in Table 4, it follows that the value of the complexation enthalpy between ammonium salts and crown ethers is influenced by the presence of a benzo group attached to the ligand (e.g., B18C6 and DB18C6). The benzo groups reduce the flexibility of the crown ether and the basicity of the ether donor atoms located next to them. Both of these effects influence the reaction enthalpy.

More important, a significant influence of the anion on the reaction enthalpy has been noted from the complex formation of different ammonium salts with crown ethers and [2.2.2] cryptand. In order to double check the validity of these results concerning the influence of the anion, competitive reactions have been carried out.

Taking into consideration the supposition that the salt forms ion pairs, the following reaction occurs during the titration of the preformed ammonium complex with 18C6 and the [2.2.2] cryptand [185]:

$$[2.2.2] + (NH_4^+ + A^- \subset 18C6) \Leftrightarrow 18C6 + (NH_4^+ \subset 2.2.2) + A^- \qquad (3.1)$$

As a consequence the cryptand [2.2.2] encapsulates the ammonium ion. The formation of ion pairs is possible including the macrocyclic ligand [198]. Contrarily, the macrobicyclic ligand [2.2.2] encapsulates the cation completely and, as a result, the existing ion pairs dissociate [199, 200]. This dissociation is accompanied by an additional reaction enthalpy $\Delta H_{\text{ion-pair}}$. Thus, the reaction enthalpy for this competitive reaction, ΔH_{comp}, is the following:

$$\Delta H_{\text{comp}} = \Delta H_{[2.2.2]} - \Delta H_{18C6} - \Delta H_{\text{ion-pair}} \qquad (3.2)$$

Using the individual reaction enthalpies for the complexation of ammonium salts with the macrocyclic ligand 18C6 and the macrobicyclic ligand [2.2.2] it is possible to calculate the reaction enthalpy for the competitive reaction. The differences between experimental and calculated reaction enthalpies can be attributed to the dissociation of the ion pair, with respect to the fact that in the case of ammonium ion, hydrogen bonds are formed between the ammonium ion and the donor atoms of the ligands.

Table 5: The calculated and measured reaction enthalpies ΔH (kJ/mol) for the competitive reaction of the ammonium salt complexes with 18C6 by the ligand [2.2.2] in chloroform at $T = 298.15$ K.

18C6 ⊂ *Ammonium salt*	$-\Delta H_{comp}$ (*experimental*)	$-\Delta H_{comp}$ (*calculated*)
$18C6 \subset C_4H_8NC(S)S^-NH_4^+$	36.3 ± 0.1	46.2 ± 8.6
$18C6 \subset (C_6H_5CH_2)_2NC(S)S^-NH_4^+$	35.9 ± 1.0	35.4 ± 2.8
$18C6 \subset (C_2H_5)_2NC(S)S^-NH_4^+$	37.5 ± 0.7	67.1 ± 2.2

The experimental data presented in Table 5 point out that in the case of ammonium dibenzyldithiocarbamate the value of ΔH_{comp} (*experimental*) is identical with ΔH_{comp} (*calculated*). Equation (1.75) entails that presumable dissociation energies of the ion pairs or hydrogen bonds do not actually exist.

Along the same line, the dissociation energies in the case of ammonium 1-pyrrolidinedithiocarboxylate are low and quite often included in the experimental errors. In contrast, the influence of anion in the case of ammonium diethyldithiocarbamate is significant.

Table 6: The calculated and measured reaction enthalpies ΔH (kJ/mol) for the competitive reaction of the ammonium salt complexes with B18C6 and DB18C6, respectively, by the [2.2.2] ligand in chloroform at $T = 298.15$ K.

Ligand* ⊂ *Ammonium salt	$-\Delta H_{comp}$ (*experimental*)	$-\Delta H_{comp}$ (*calculated*)
$B18C6 \subset C_4H_8NC(S)S^-NH_4^+$	59.9 ± 1.7	78.4 ± 13.7
$B18C6 \subset (C_6H_5CH_2)_2NC(S)S^-NH_4^+$	55.4 ± 3.6	52.7 ± 6.1
$B18C6 \subset (C_2H_5)_2NC(S)S^-NH_4^+$	63.3 ± 0.2	91.0 ± 4.0
$DB18C6 \subset C_4H_8NC(S)S^-NH_4^+$	64.2 ± 2.4	105.5 ± 15.0
$DB18C6 \subset (C_6H_5CH_2)_2NC(S)S^-NH_4^+$	58.7 ± 4.0	57.9 ± 12.0
$DB18C6 \subset (C_2H_5)_2NC(S)S^-NH_4^+$	70.9 ± 3.6	94.5 ± 2.9

The same procedure was also used in the case of the macrocyclic ligands benzo 18-crown-6 and dibenzo 18-crown-6. The results presented in Table 6 confirm the data observed and listed in Table 5, namely, the value of ΔH_{comp} (*experimental*) is quite identical with ΔH_{comp} (*calculated*) for ammonium dibenzyldithiocarbamate, $(C_6H_5CH_2)_2NC(S)S^-NH_4^+$. What makes the difference between Table 5 and Table 6 refers to ammonium 1-pyrrolidinedithiocarboxylate, $C_4H_8NC(S)S^-NH_4^+$, for which the difference in the values of the reaction enthalpy is significant.

Following the results obtained for the reaction enthalpies by competitive reaction using [2.2.2] cryptand, the experiments were repeated with the ligand 18C6 instead of cryptand [2.2.2]. The calculated and measured reaction enthalpies for the competitive reaction of the ammonium salt complexes with B18C6 and DB18C6, respectively, by crown ether 18C6 in chloroform at T = 298.15 K are summarized in Table 7.

Table 7: The calculated and measured reaction enthalpies ΔH (kJ/mol) for the competitive reaction of the ammonium salt complexes with B18C6 and DB18C6, respectively, by the ligand 18C6 in chloroform at $T = 298.15$ K.

Ligand ⊂ Ammonium salt	$-\Delta H_{comp}$ (*experimental*)	$-\Delta H_{comp}$ (*calculated*)
B18C6 ⊂ $C_4H_8NC(S)S^-NH_4^+$	15.7 ± 1.4	32.2 ± 11.9
B18C6 ⊂ $(C_6H_5CH_2)_2NC(S)S^-NH_4^+$	11.3 ± 3.0	17.3 ± 6.9
B18C6 ⊂ $(C_2H_5)_2NC(S)S^-NH_4^+$	10.6 ± 0.9	23.9 ± 3.2
DB18C6 ⊂ $C_4H_8NC(S)S^-NH_4^+$	93.6 ± 8.8	59.3 ± 13.2
DB18C6 ⊂ $(C_6H_5CH_2)_2NC(S)S^-NH_4^+$	21.9 ± 7.8	22.5 ± 12.8
DB18C6 ⊂ $(C_2H_5)_2NC(S)S^-NH_4^+$	22.5 ± 3.4	27.4 ± 2.1

From the results presented in Table 7, one can observe a very good agreement between the values of ΔH_{comp} (*calculated*) and ΔH_{comp} (*experimental*) for the competitive reactions of ammonium dibenzyldithiocarbamate $(C_6H_5CH_2)_2NC(S)S^-NH_4^+$.

In order to get more information about the reaction enthalpy, ΔH, for the complex formation of ammonium salts with the crown ether 18C6 and cryptand [2.2.2], different solvents were used as reaction medium. The complexation enthalpies are given in Table 8.

The complexation enthalpy of ammonium diethyldithiocarbamate with cryptand [2.2.2] obtained in 1,2-dichloroethane is identical with the one obtained in chloroform.

Table 8: Reaction enthalpies ΔH (kJ/mol) for the complex formation of ammonium salts with 18C6 and [2.2.2] cryptand, as well as calculated and measured reaction enthalpies for the competitive reaction of the ammonium salt complexes with 18C6 by the ligand [2.2.2] in 1,2-dichloroethane at $T = 298.15$ K.

Ammonium salt	$-\Delta H_{[2.2.2]}$	$-\Delta H_{(18C6)}$	$-\Delta H_{comp}$ (*experimental*)	$-\Delta H_{comp}$ (*calculated*)
$C_4H_8NC(S)S^-NH_4^+$	97.6 ± 2.4	7.2 ± 1.2	66.6 ± 1.5	90.4 ± 3.6
$(C_2H_5)_2NC(S)S^-NH_4^+$	96.1 ± 1.8	12.5 ± 1.7	67.7 ± 0.8	83.6 ± 3.5

It was observed that the experimental value of the reaction enthalpy ΔH_{comp} (*experimental*) (kJ/mol) for the competitive reaction of the ammonium salt complexes with 18C6 by the cryptand [2.2.2] (eq. 1.74) in the same reaction medium is identical in all cases. In order to support this observation, further experiments were carried out in dichloromethane and dioxane ($\varepsilon_r = 2.21$) [201]. The results summarized in Table 9 proved the supposition made.

Tabel 9: Measured reaction enthalpies ΔH (kJ/mol) for the competitive reaction of the ammonium salt complexes with 18C6 by the ligand [2.2.2] in dichloromethane and dioxane at $T = 298.15$ K.

Medium	***Ammonium salt***	$-\Delta H_{comp}$ (*experimental*)
CH_2Cl_2	$C_4H_8NC(S)S^-NH_4^+$	57.6 ± 0.6
	$(C_6H_5CH_2)_2NC(S)S^-NH_4^+$	57.5 ± 1.2
	$(C_2H_5)_2NC(S)S^-NH_4^+$	57.2 ± 3.1
$C_4H_8O_2$	$C_4H_8NC(S)S^-NH_4^+$	44.4 ± 1.7
	$(C_6H_5CH_2)_2NC(S)S^-NH_4^+$	36.0 ± 3.2
	$(C_2H_5)_2NC(S)S^-NH_4^+$	44.4 ± 2.2

3.5 Conclusion - Complexes of crown ethers and cryptands with cations

The influence of the solvent polarity upon the complex formation between crown ethers with cations has been investigated. By using mixtures of water-dioxane, it has been possible to study the complex formation behavior of 18C6 with cations such as ammonium and barium, respectively, over a large range of dielectric constant value of the reaction medium.

With the increase of dioxane concentration, the values of the stability constants and reaction enthalpies for the complex formation of 18C6 with ammonium perchlorate in a mixture of water and dioxane at various proportions increase as well.

Consequently, the reaction enthalpy values ΔH of the complex formation between 18C6 and ammonium perchlorate in a mixture of dioxane in water, monotonously decrease with the increase in the dielectric constant. The variability of the reaction entropies is not significant over the full range of dioxane concentration.

From the plots of the complexation enthalpies between 18C6 with barium and ammonium perchlorate, respectively, on the concentration of dioxane in water, it can be seen that the slopes are different. In case of the ammonium ion not only electrostatic interactions ensue but also hydrogen bonds are formed between the ammonium ion and the donor atoms of the ligands. In this case the values of the reaction enthalpies are not comparable with those for the alkali ions.

The logarithms of the stability constants, log *K*, the reaction enthalpies, ΔH , and the reaction entropies, ΔS , for the complexation of alkali metal cations like Na^+, K^+, Rb^+, and Cs^+ as dibenzyldithiocarbamate salts in chloroform by crown ethers, such as 12C4, B12C4, 15C5, B15C5, DB15C5, and 18C6 obtained by calorimetric titrations, are fairly high. The experimental results presented here indicate that the complexation is favored by the enthalpic contributions.

The stability constants for complexes of 15C5, B15C5, and DB15C5 with Na^+ could not be calculated from the calorimetric titrations. Likewise the stability constants were not possible to be calculated from thermograms in the case of 18C6 complexes with alkali metal cations since their logarithmized values are log K > 5.

A decreasing monotonicity of the dependence in the reaction enthalpy on the cation radius for the complex formation between crown ethers and alkali metal cations in chloroform has been observed. The reaction entropy under the experimental conditions depends on the ligand nature only.

The ion-dipole interactions are responsible for complexation behavior of crown ethers with alkali metal cations. Also, the addition of benzo group to the ligand (e.g., B12C4, B15C5, DB15C5) leads to decrease of reaction enthalpies. The explanation is given by the ligand rigidity that rises by successive addition of benzo groups, which gradually decreases the ligand flexibility. Likewise the basicity of donor oxygen atoms decreases when attached to the benzo group. As a result, the strength of the interaction is reduced.

Further, the reaction entropies decrease when a benzo group is attached to the ligand (e.g., B12C4 and B15C5). When a second benzo group is added, the reaction entropy continues to decrease by about the same amount (e.g., DB15C5). The explanation is similar to the one given in the case of the reaction enthalpy presented above.

The values of the reaction enthalpies for complex formation of ammonium salts with [2.2.2] cryptand are higher compared to the corresponding values of complex formation of ammonium salts with ligands 18C6, B18C6, and DB18C6. This is due to the number of donor atoms of the ligand [2.2.2], which is higher than that of the crown ethers under study.

The enthalpy of complexation between ammonium salts and crown ethers is influenced by the presence of benzo group attached to the ligand (e.g., B18C6 and DB18C6). The nature of the anion associated to the ammonium ion has a significant influence upon complexation of ammonium with ligands. In this respect competitive reactions were carried out.

The effect of solvent on the enthalpy of complex formation between ammonium salts with crown ethers and [2.2.2] cryptand was also studied. Thus, the enthalpy for complex formation of ammonium diethyldithiocarbamate with [2.2.2] cryptand in 1,2-dichloroethane is identical with the one obtained in chloroform.

The value of the experimental reaction enthalpy ΔH_{comp} (kJ/mol) for the competitive reaction of the ammonium salt complexes with 18C6 by the [2.2.2] cryptand in the same reaction medium is identical in all cases. In order to support this observation, further experiments have been carried out in dichloromethane and dioxane and the results have confirmed this finding.

4 Influence of polar solvents upon the complex formation of crown ethers and cryptands with cations in halogenated organic solvents

4.1 Introduction

The medium effects are of particular interest for complexation equilibria in several aspects, such as the discrimination of different types of interaction mechanisms, in searching the optimal conditions for binding and establishing suitable conditions for solubility problems [25]. Usually, the presentation of solvent effects takes into account the electrostatic forces only and considers the solvent as an inert continuous medium characterized by the dielectric constant, ε.

However, the solute-solvent interactions encompass several contributions from non-specific electrostatic interactions (ion-ion, ion-dipole, dipole-dipole, induced dipoles, etc.) to specific electron or proton donor-acceptor interactions and solvophobic interactions [25]. In this respect, the influence of the solvent on a variety of chemical phenomena, including solubility, phase transfer, and chemical equilibria and kinetics [202-204] are among the most important. Recently, significant progress has been made in theoretical calculations of free energies of solvation [25]. In aqueous solution, most of the crown ethers are less selective and their complexes are less stable than in less polar solvents. For instance, the stability of the complex between K^+ and 15C5 increases when the solvent is changed from water to methanol or acetonitrile [205, 206]. Moreover, the studies [207] on the interaction of Na^+ with 15C5 and 18C6 in mixed methanol-water solvents as function of methanol:water composition revealed that replacement of water by methanol led to an increase in complex stability.

It is well-known from previously reported investigations that 18C6 forms stable complexes with several molecules like water, acetonitrile, methanol, etc., through hydrogen bonds and dipolar forces. The study of this kind of interactions between crown ethers and these molecules is important for a better understanding of the mechanism of biological transport, molecular recognition, enzyme specific binding aspects, as well as extraction abilities of crown ethers [208-211].

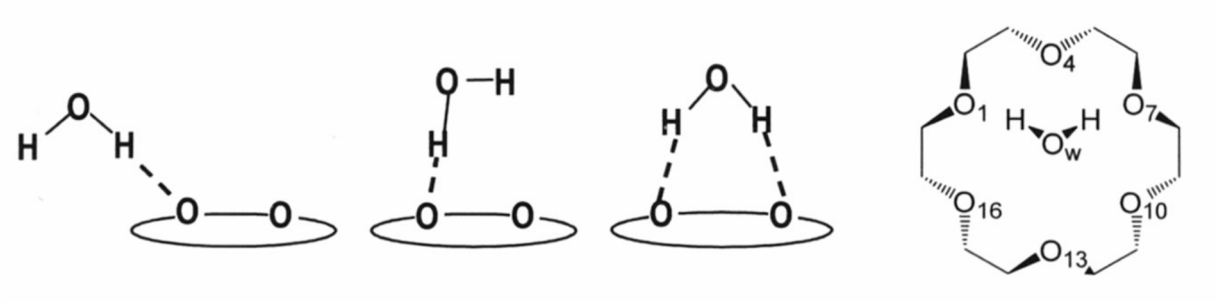
The stability and selectivity of cation binding is determined by the interaction of the cation both with the solvent and the crown ether. Thus, if the solvent medium is changed, the significant effect on the binding constant is observed especially where cations are strongly solvated in one solvent and not in another [212]. In view of a deeper insight into the effects of solvent on the stabilities of complexes formed, several thermodynamic measurements were performed [213]. These experiments indicated that the selectivity of crown ethers towards alkali and alkaline earth metal ions is dependent on the solvent. Also, the relative stability of a complex was reported to increase with the decrease in the solvating power [213].

Wipff *et al*. [214-217] studied the water-binding mode to the crown ether 18C6 (monodentate and bidentate hydrogen bonds), by using molecular dynamic simulations. These results revealed the importance of dynamics and the surrounding medium on conformational and hydrogen-bonding properties of 18C6 (Figure 30).

The inclusion of water molecules in complexes was noticed for several polyethers, where one water molecule only is bound to the host macrocycle [76, 78]. The computer simulation

studies by Kowall and Geiger [218], and by Thompson [219] showed that 18C6 in water binds two water molecules by double hydrogen bonding, and 15C5 is hydrated mostly by a single hydrogen-bonded water molecule. This conclusion was confirmed by IR spectroscopic studies [220, 221]. On the other hand, these authors underlined that the hydrophobic hydration of 18C6 is important in governing the conformational dynamics of this ligand in aqueous solutions, while the *ab initio* [222] studies indicated that the cooperative electrostatic interactions are responsible for the hydration pattern of 18C6 in aqueous solutions.

X-ray diffraction [223, 224] and Raman spectroscopic [225] studies revealed that 18C6 forms various hydrates (1:4, 1:6, 1:8, and 1:12) in solid state.



a) b) c) d)

Figure 30: Schematic representation of single-out (a), single-in (monodendate) (b), and bridging (bidendate) (c) of H_2O to 18C6, and of the D_{3d} bridging hydrate (d) [216].

The study on complexation of crown ethers and cryptands with cations such as alkali metal and ammonium ion in chloroform carried out in Chapter 3 is continued here with the investigations on polar solvents influence on these complexes.

4.2 Reaction enthalpy of complex formation between crown ethers and water in chloroform

The experimental reaction enthalpy ΔH_{exp} determined from the heat provided by the calorimetric measurement of the complex formation between 18C6 and water in chloroform can be expressed as:

$$\Delta H_{exp} = \Delta H_{reaction} + \sum_{i=1}^{n} \Delta H_i \qquad (4.1)$$

where $\Delta H_{reaction}$ is the reaction enthalpy of complex formation between 18C6 with water in chloroform and $\sum_{i=1}^{n} \Delta H_i$ is the sum of all the other enthalpic processes which may possibly occur during the complexation process (e.g., heat of mixing, heat of dilution of ligand, heat of dilution of salts, etc.). In the case of:

$$\sum_{i=1}^{n} \Delta H_i \approx 0 \qquad (4.2)$$

the reaction enthalpy takes the form:

$$\Delta H_{reaction} = \Delta H_{exp} \tag{4.3}$$

Several test titrations were performed in order to ensure that the heat effects upon complexation of water by 18C6 express the interaction between 18C6 and water only. Thus, to avoid the effects of the heat resulted from the mixing of chloroform with a solution of water in chloroform (which could appear during titration), pure chloroform was titrated in a solution of water in chloroform. Given the water solubility in chloroform [226-229], the experiments were carried out with water concentrations between $0.01 - 0.1$ mol/l. According to these experiments, the heat effects found were < -1 kJ/mol. The same result in terms of the heat effects (i.e., < -1 kJ/mol) was obtained in the case of titrating a solution of water in chloroform into pure chloroform.

The heat of dilution of 18C6 (< -1 kJ/mol) was measured from the titration of a solution of ligand in chloroform (ε = 4.90) [201] into pure chloroform and from the titration of pure chloroform into a solution of ligand in chloroform. To obtain information about the complex composition, the calorimetric titration experiments between the ligand and water were studied under the conditions of 1:1 complex stoichiometry.

Under the different experimental conditions considered, it is obvious (within the experimental errors) that $\Delta H_1 \approx \Delta H_2$, which led to the conclusion that a $1:1$ complex formation was likely to occur between 18C6 and water in chloroform. In a similar approach, Kikuchi *et al.* [230], by plotting the increments of the water concentration in the organic phase (e.g., chloroform) as a function of the concentration of the ligand (e.g., B18C6) in the organic solvent, derived the stoichiometry 1:1 for the ligand:water complex from the slope of the plot.

In Figure 31, the reaction enthalpy, ΔH (kJ/mol), obtained for the titration of a solution of water in chloroform into a solution of 18C6 in chloroform at different concentrations is presented. The slope of the regression (best fit) line gives the measure of linear correlation.

As one can see, the values obtained for the reaction enthalpies depend on the water concentrations, and they are not influenced by the use of different concentrations of 18C6. The hydrogen bonds and dipole-dipole interactions are responsible for the complex formation between water molecules and donor centers of the 18C6 macroring. The size of the water molecule (approximate diameter of 2.8 Å if one assumes a sphere [231]) is in agreement with the cavity size of the 18-membered ring crown ether (2.9 ± 0.3 Å) [232] and is too large for that of the 15-membered ring crown ether (2.0 ± 0.2 Å) [232]. In this respect, the 18-membered ring crown ether should be suitable for double hydrogen bonding with the water molecule, while the 15-membered ring crown ethers are too small for this type of bonding [230].

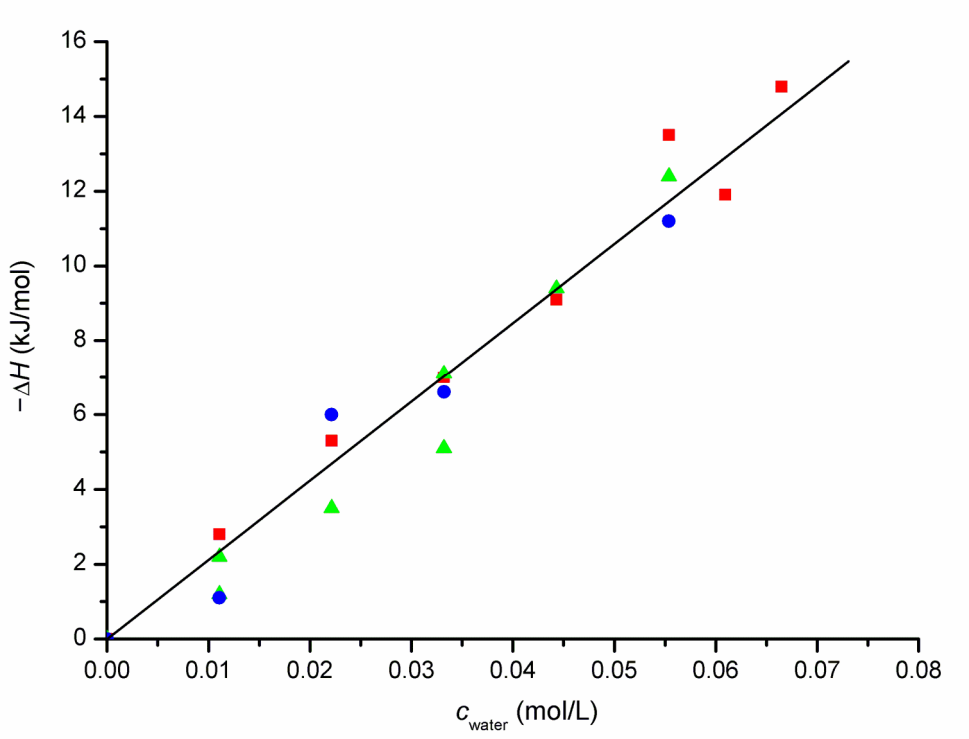


Figure 31: Quantitative functional relationship between the reaction enthalpy ΔH for complex formation of 18C6 and water at various water concentrations in chloroform at $T = 298.15\,K$, and for c_{18C6} (mol/L) = 0.02 (■), 0.04 (▲), and 0.08 (●).

Following the same sequence of steps as described above, the values of the reaction enthalpy, ΔH, for the complex formation between 12C4, 15C5,18C6, and B18C6, respectively, and water in chloroform were measured. The strength of linear correlation between the reaction enthalpy and water concentration for each ligand is summarized in Table 10. From the data specified in this table, a decreasing in the slope of the regression line is noticeable along with a decrease in the ring size of the crown ether.

The hydration of crown ethers in chloroform obtained in the present study (Table 10) is in good agreement (i.e., the same order of magnitude) with the results obtained from the studies of hydration of crown ethers in the gas phase [233].

The reaction enthalpy ΔH for the complex formation between B18C6 and water in chloroform is smaller than its counterpart obtained in the reaction of 18C6 and water, even though both crown ethers have similar dimensions of their cavity. This effect is attributed to the benzo substitution in the macrocyclic ring of 18C6, which reduces the basicity of the oxygen atoms attached to the benzo rings and the flexibility of the crown ether. As a result, the strength of the interaction is reduced.

Table 10: Dependence of the strength of linear correlation between the reaction enthalpy and water concentration for complex formation between crown ethers and water in chloroform at $T = 298.15$ K on their cavity rings.

Crown ether	***Cavity Size*** (Å)[a]	$-\Delta H/c_{\mathrm{Water}}$ (kJ L mol^{-2})
18C6	1.34 – 1.55	211.7 ± 5.7
B18C6	1.34 – 1.55	152.7 ± 4.2
15C5	0.86 – 0.92	92.6 ± 6.4
12C4	0.60 – 0.75	28.7 ± 6.1

[a] From Ref.[98]

In Figure 32, the reaction enthalpy for the complex formation between crown ethers and water is plotted against water concentration in chloroform at T = 298.15 K.

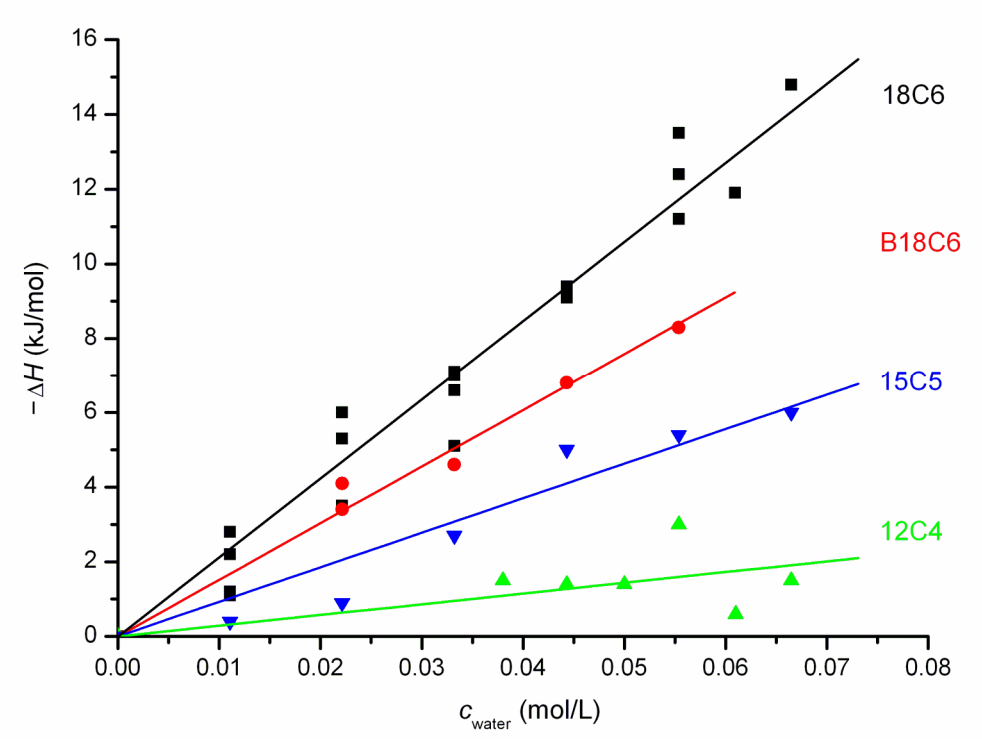


Figure 32: Linear correlation of the reaction enthalpy ΔH for complex formation of crown ethers: 18C6 (—■—), B18C6 (—●—), 15C5 (—▼—) and 12C4 (—▲—) with water, and water concentration in chloroform at $T = 298.15$ K.

The results obtained for the reaction enthalpies of the complex formation between 12C4, 15C5, and 18C6 and water in dichloromethane ($\varepsilon = 8.93$ [201]) are presented in Table 11.

Table 11: Dependence of the strength of linear correlation between the reaction enthalpy for complex formation between crown ethers and water in dichloromethane at $T = 298.15$ K on the ring size of the ligand cavity.

Crown ether	***Radius*** (Å)[a]	$-\Delta H/c_{\text{Water}}$ (kJ L mol^{-2})
18C6	1.34 – 1.55	158.0 ± 5.2
15C5	0.86 – 0.92	62.1 ± 4.9
12C4	0.60 – 0.75	5.1 ± 2.8

[a] From Ref. [98].

The enthalpy ΔH for complex formation between crown ethers and water studied in dichloromethane is smaller than the corresponding one obtained in chloroform. As observed from Figure 33, the reaction enthalpic effects decrease along with a decrease in the size of the crown ether.

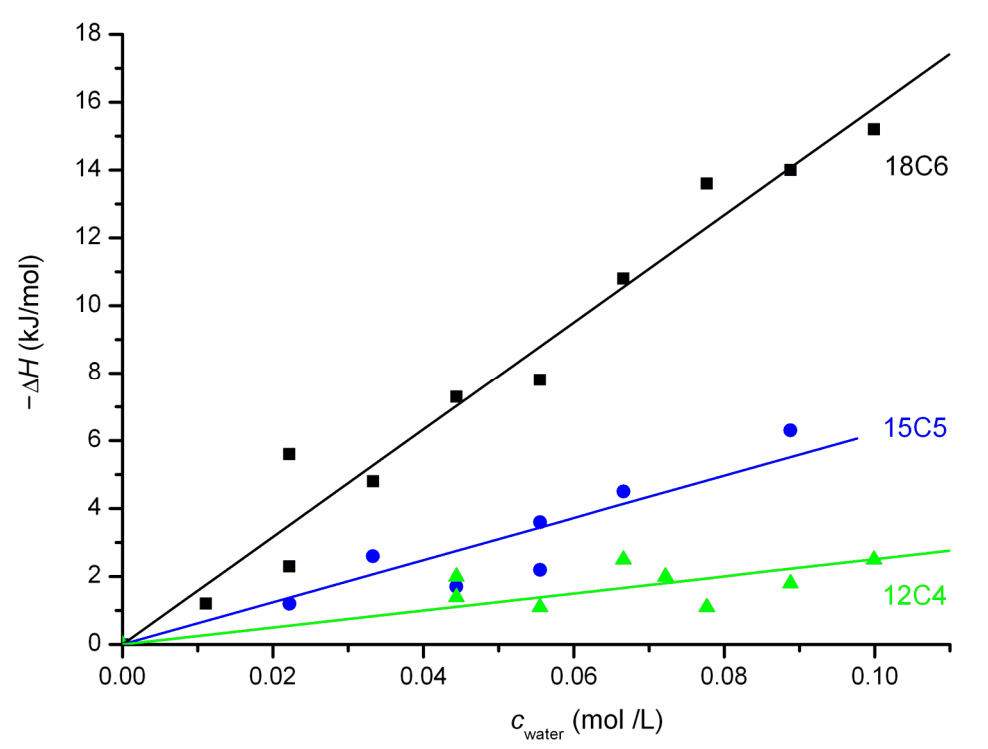


Figure 33: Enthalpy ΔH for complex formation between crown ethers: 18C6 (—■—), 15C5 (—●—), and 12C4 (—▲—), and water as function of water concentration in dichloromethane at $T = 298.15$ K.

In order to unravel more explicitly the influence of the reaction medium on the complexation between 18C6 and water, the chloroform and dichloromethane were replaced with the following halogenated solvents: carbon tetrachloride ($CCl_4, \varepsilon = 2.238$ [201]), and 1,2-dichloroethane ($ClCH_2CH_2Cl$, $\varepsilon = 10.36$ [201]).

Table 12: Dependence of the strength of linear correlation between the reaction enthalpy for complex formation between 18C6 and water on the nature of different organic solvents at $T = 298.15$ K.

Solvent	$-\Delta H/c_{\text{Water}}$ (kJ L mol^{-2})
CCl_4	200.1 ± 11.6
$ClCH_2CH_2Cl$	63.8 ± 2.1

For the reaction of 18C6 with water in all above mentioned halogenated solvents, the value of reaction enthalpy ΔH for the complex formation between 18C6 and water at a given concentration of water c_{water} decreases following the sequence: $CCl_4 > CH_2Cl_2 > ClCH_2 - CH_2Cl$ (Figure 34).

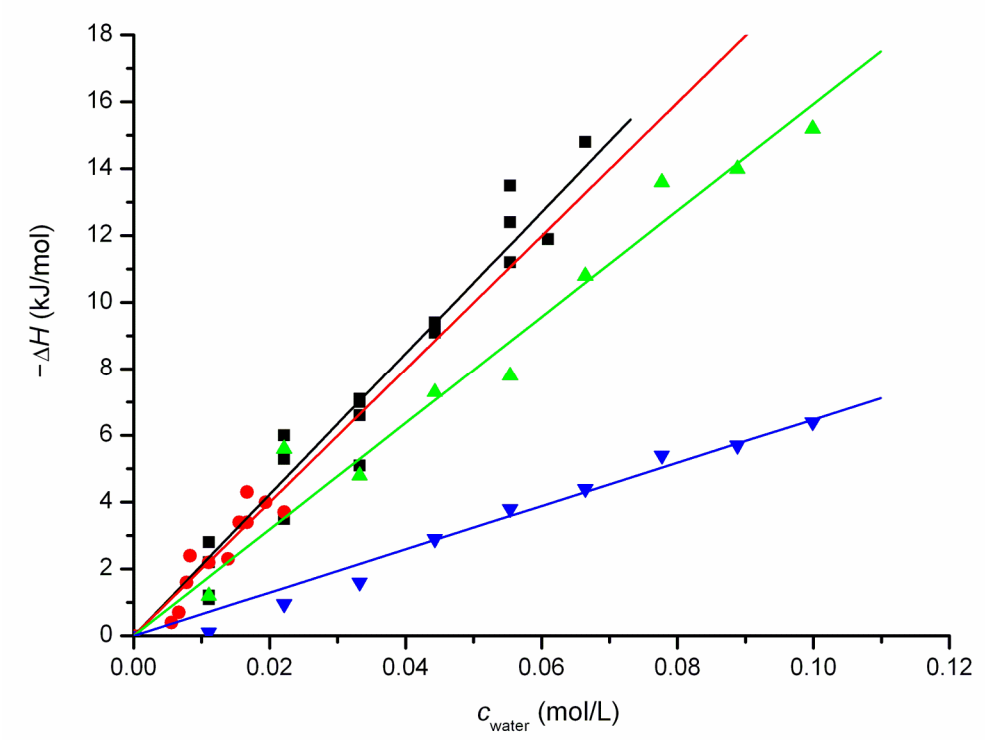


Figure 34: Reaction enthalpy ΔH for complex formation of 18C6 with water in halogenated solvents: chloroform (—■—), carbon tetrachloride (—●—), dichloromethane (—▲—), 1,2-dichloromethane (—▼—), at $T = 298.15$ K as a function of water concentration.

4.3 Reaction enthalpy of complex formation between crown ethers and methanol, acetone, and acetonitrile in chloroform

In order to obtain more information about the complex formation between 18C6 and various less polar solvents than water, such as methanol ($\varepsilon = 32.70$ [201]), acetone ($\varepsilon = 37.5$ [201]), and acetonitrile ($\varepsilon = 20.70$ [201]) in chloroform, further investigations were made. The

results are presented in Table 13, which show the quantitative relationship between the reaction enthalpy for complex formation between 18C6 and different polar solvents in chloroform at 298.15 K with concentrations within the range $[0.0 - 0.1]$ mol/L.

Table 13: Dependence of the correlation between the reaction enthalpy and solvent concentration for complex formation between 18C6 with methanol, acetone, and acetonitrile in chloroform at $T = 298.15$ K on the nature of the solvent.

Solvent	$-\Delta H/c_{\text{Solvent}}$ (kJ L mol^{-2})
CH_3OH	< 1
CH_3COCH_3	11.4 ± 2.7
CH_3CN	< 1

The experimental results presented in Table 13 show that for complex formation between 18C6 and methanol and acetonitrile in chloroform, the value of $-\Delta H/c_{\text{Solvent}} < 1$ (kJ L mol^{-2}) for both solvents, even though the methanol is able to donate hydrogen bonds. As an aprotic solvent, the acetonitrile exhibits weaker donor ability than water and it is unable to form hydrogen bonds with the oxygen atoms of 18C6. From literature, it is known that 18C6 forms complexes with acetonitrile by dipole-dipole interactions in the crystal [234] and in solution [235].

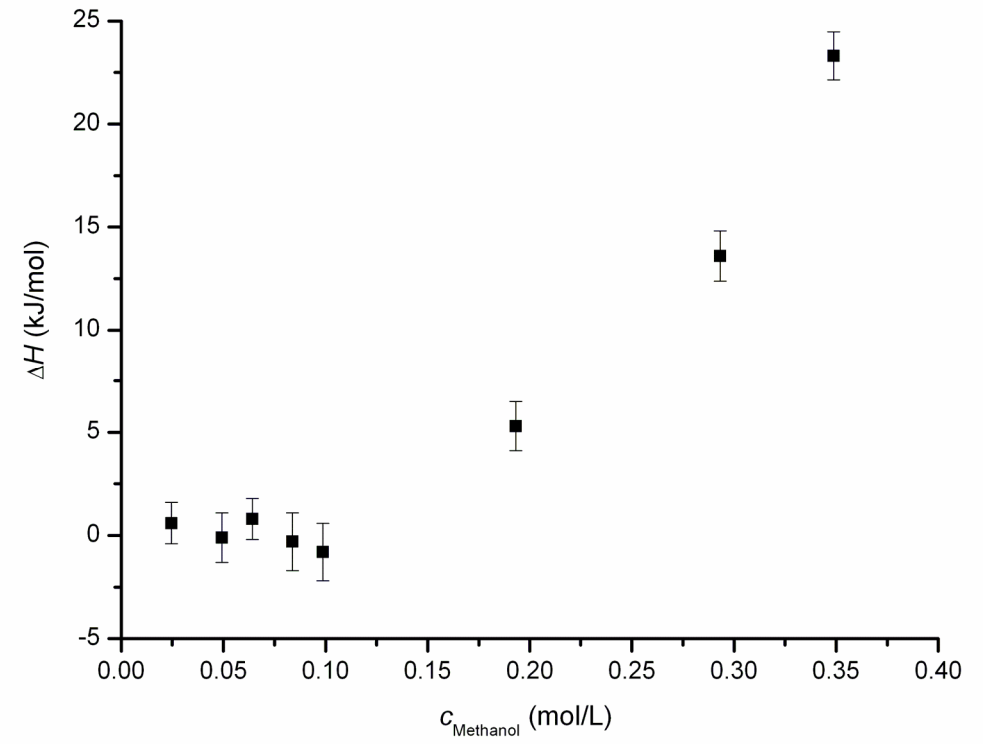


Figure 35: Reaction enthalpy of complex formation between 18C6 and methanol as function of various methanol concentration in chloroform at $T = 298.15$ K.

Figure 35 shows that ΔH remains constant for methanol concentrations within the range $0.0 - 0.1$ mol/L, whereas a significant change occurs at concentrations higher than 0.1 mol/L. For the plateau, where there is no significant change in the reaction enthalpy for complex formation between 18C6 and methanol in chloroform due to methanol concentration, a homogeneous mixture of complex of 18C6 with methanol and chloroform is likely to exist. A possible explanation for the increase in the reaction enthalpy at higher values of methanol concentration lies in the formation of small methanol clusters in the form of aggregates within chloroform. If this is true, it may constitute the framework of studying the solvation of 18C6 in methanol.

4.4 Water influence on the complexation of crown ethers with cations in chloroform

It is of special interest how the water molecules control structure, reactivity, molecular recognition, and dynamics, with particular emphasis on biological system [236]. The effect of very small amounts of water on the complex formation between 18C6 or [2.2.2] cryptand and K^+ in chloroform was studied by calorimetric titrations [184, 237] establishing that the water molecules have a pronounced effect on the complex formation.

Similar results were obtained by computer simulations using molecular dynamics performed by Wipff *et al*. [214-216] who studied the influence of water in the organic phase on the structure and relative binding affinities of 18C6 and its complexes. These results are important in ion separation by solvent extraction or transport through liquid membranes which involve the ion transfer between non miscible solvents.

It is known that the solubility of dibenzyldithiocarbamates is high enough for calorimetric titrations in organic solvents. In this respect, the complex formation of 18C6 with potassium dibenzyldithiocarbamate salt in chloroform in the presence of different water concentrations has been studied. The reaction enthalpy for the complex formation between 18C6 and potassium dibenzyldithiocarbamate in chloroform has the value $\Delta H = -71.2$ (kJ/mol). The values of the reaction enthalpy of complex formation between 18C6 and potassium dibenzyldithiocarbamate in chloroform in the presence of different concentrations of water are presented in Table 14.

Table 14: Reaction enthalpy ΔH (kJ/mol) for complex formation of 18C6 ($c = 0.02$ mol/L) with potassium dibenzyldithiocarbamate ($c = 0.002$ mol/L) in chloroform and different concentrations of water at 298.15 K.

c_{water}	$-\Delta H$	$c_{K^+} : c_{\text{water}}$
0.0000	71.2 ± 0.5	1:0.0
0.0055	67.5 ± 1.3	1:2.3
0.0111	64.2 ± 0.9	1:4.6
0.0166	61.1 ± 1.2	1:6.6
0.0221	58.8 ± 1.1	1:8.9
0.0277	53.5 ± 0.7	1:11.6
0.3322	47.2 ± 1.4	1:13.8
0.0388	41.1 ± 0.8	1:15.4
0.0443	30.9 ± 1.3	1:17.6

From the results summarized in Table 14, one can see that $-\Delta H$ decreases with the increase in water concentration.

In order to highlight the influence of the $c_{K^+} : c_{\text{water}}$ ratio on reaction enthalpy, the roles have been reversed, namely, the water concentration has been kept constant and the potassium dibenzyldithiocarbamate concentration has been varied during the calorimetric titration of 18C6 into a chloroform solution of potassium dibenzyldithiocarbamate and water. The obtained results are summarized in Table 15.

Table 15: Reaction enthalpy ΔH (kJ/mol) for complex formation of 18C6 ($c = 0.02$ mol/L) with potassium dibenzyldithiocarbamate ($c = 1.3\times10^{-3} - 2.5\times10^{-3}$ mol/L) in chloroform and water (constant concentration, $c_{\text{water}} = 0.39$ mol/L) at $T = 298.15$ K.

c_{K^+}	$-\Delta H$	$c_{K^+} : c_{water}$
0.0025	40.5 ± 0.9	1:15.4
0.0023	39.9 ± 1.1	1:16.9
0.0022	41.5 ± 0.8	1:17.6
0.0019	38.2 ± 1.2	1:20.5
0.0016	40.8 ± 0.7	1:24.7
0.0014	41.7 ± 1.2	1:28.2
0.0013	42.7 ± 1.0	1:29.7

As the data presented in Table 15 clearly point out, the variation of salt concentration, that is, the variation of $c_{K^+} : c_{water}$ is not really affecting the reaction enthalpy ΔH. By titration of K^+ cation in chloroform and water with 18C6 in chloroform and 18C6 in chloroform and water, the obtained results indicated no difference for the ΔH values of complex formation between 18C6 and K^+ cation.

In Table 16, the ΔH for complex formation of alkali metal cations such as Na^+, Rb^+, and Cs^+ dibenzyldithiocarbamate salts and NH_4^+– with 18C6 in chloroform and water at different concentrations have been compiled. The results clearly show that in the case of complex formation between NH_4^+ cation with 18C6 in chloroform, the water is not influencing the value of ΔH.

Table 16: Reaction enthalpy ΔH (kJ/mol) of complex formation of 18C6 with alkali dibenzyldithiocarbamate salts and ammonium 1-pyrrolidinedithiocarboxylate in chloroform at different concentrations of water at $T = 298.15$ K.

Cation	c_{water} (mol/L)	$-\Delta H$	$c_{cationt} : c_{water}$
Na^+	0.0000	46.3 ± 0.9	1:0.0
	0.0011	43.1 ± 1.1	1:0.5
	0.0022	39.6 ± 0.9	1:1.0
	0.0033	31.5 ± 1.3	1:1.6
Rb^+	0.000	67.1 ± 0.5	1:0.0
	0.011	64.4 ± 1.0	1:6.1
	0.022	60.4 ± 1.2	1:12.2
	0.033	56.6 ± 0.9	1:18.5
	0.044	50.0 ± 0.7	1:24.5
Cs^+	0.000	58.0 ± 0.5	1:0.0
	0.011	55.8 ± 0.7	1:6.2
	0.022	54.5 ± 0.3	1:12.1
	0.033	53.3 ± 0.5	1:18.0
	0.044	51.8 ± 0.2	1:24.5
NH_4^+	0.000	117.5 ± 3.6	1:0.0
	0.011	118.8 ± 3.2	1:6.0
	0.022	115.6 ± 3.8	1:12.3
	0.033	118.1 ± 2.0	1:18.2
	0.044	116.2 ± 2.6	1:24.1

In the case of dibenzyldithiocarbamate salts of alkali metal cations a correlation between cation radius and the influence of water concentration can be observed. Thus, the smaller the cation radius, the higher is the water influence on the respective complex formation between dibenzyldithiocarbamate salt and 18C6 in chloroform.

In Figure 36, the relationship between the reaction enthalpy and water concentration of complex formation between Na^+, K^+, Rb^+, and Cs^+ dibenzyldithiocarbamates with 18C6 in chloroform and water at different concentrations at $T = 298.15$ K is presented.

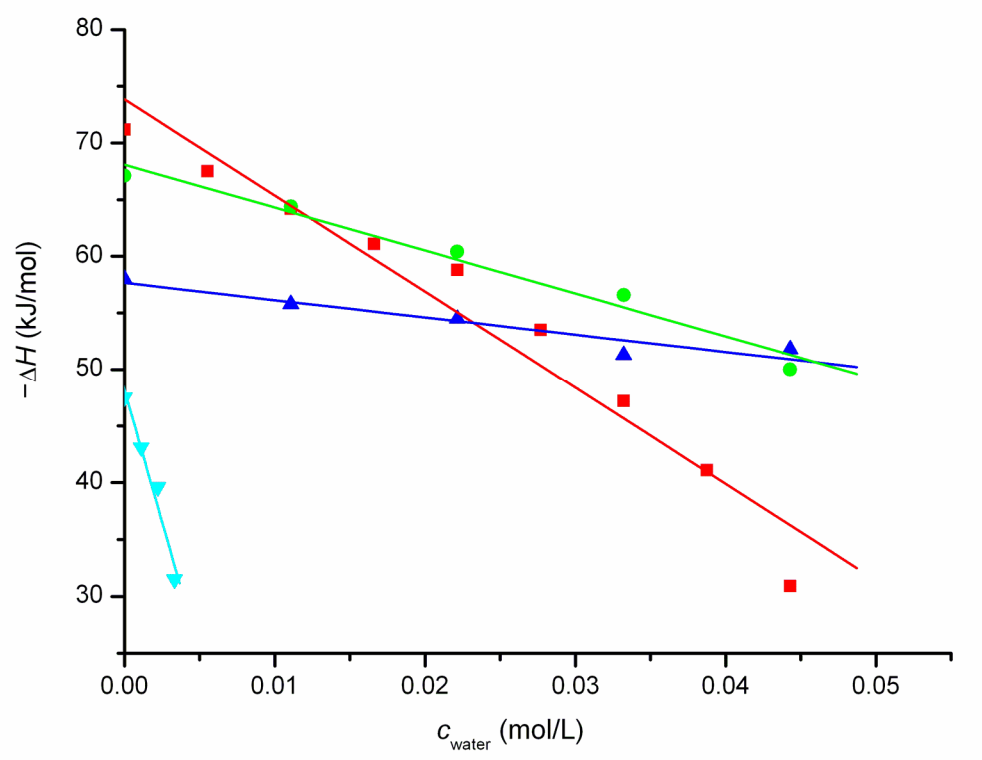


Figura 36: Water influence on the reaction enthalpy ΔH of complex formation between 18C6 and dibenzyldithiocarbamate salts of alkali cations: Na^+, $r_{Na^+} = 1.02$ Å (—▼—), K^+, $r_{K^+} = 1.38$ Å, (—■—), Rb^+, $r_{Rb^+} = 1.52$ Å (—●—), and Cs^+, $r_{Cs^+} = 1.67$ Å (—▲—) in chloroform at $T = 298.15$ K [183].

The slope of each plot correlates with the interactions between water molecules and cations. Based on the correlation observed between the cation radius and the magnitude of water influence, it is possible to check whether the interactions are (mostly) governed by their electrostatic nature (i.e., Coulombian interactions). Technically, the verification amounts to the extraction of slopes from the plots that give the water influence on the reaction enthalpy and checking with the Coulomb law:

$$F = \frac{1}{4\pi\varepsilon} \cdot \frac{|q_1 \cdot q_2|}{r^2} \tag{4.4}$$

where $\varepsilon_0 = 8.85418 \times 10^{-12}\ C^2/Nm^2$ is the dielectric permittivity *in vacuum*, ε_r is the relative dielectric permittivity of the medium, and $\varepsilon = \varepsilon_r \cdot \varepsilon_0$.

The electrostatic charge was considered uniformly spread on the ion surface, hence in its exterior the electrostatic field acts as if the whole charge would have been concentrated in its center of symmetry according to the Gauss law. Further, the effects of first order were considered only, that is, the radii of cations are the only significant measures of inverse squares. Here, this working hypothesis holds best for Na^+, yet all cations involved have radii within the range 1 to 2 Å that makes sense. The results were plotted in Figure 37, which indicates a good agreement of the interaction magnitude with the inverse of the square distance between the charge centers. Moreover, Cs^+ is close to 0 according to our previous observations concerning the insensitivity of Cs^+ to the solvent nature (i.e., the enthalpy of its complexation reaction is not significantly affected by adding water to chloroform). Contrarily, the values for Rb^+, K^+, and Na^+ should align along a straight line. Apart from the measurement errors, a perfect straight line would be unrealistic implying that, by adding water to chloroform, the only interactions between the ligand and salt influencing the reaction enthalpy to be of electrostatic nature. There are nevertheless forces of different origin than the Coulombian attraction, which are responsible for the deviations from a straight line. The approximate linearity proves by all means that the electrostatic interactions are predominant in the complexation reactions of ligands with cations in polar solvents.

Besides, the large metal ions like Cs^+ and Rb^+ are not fully accommodated in the cavity of 18C6 and much of their surface contacts with water molecules. Though the interactions between the alkali ions and water molecules are weak, the effect is increasing with the increasing radius such as $K^+ < Rb^+ < Cs^+$.

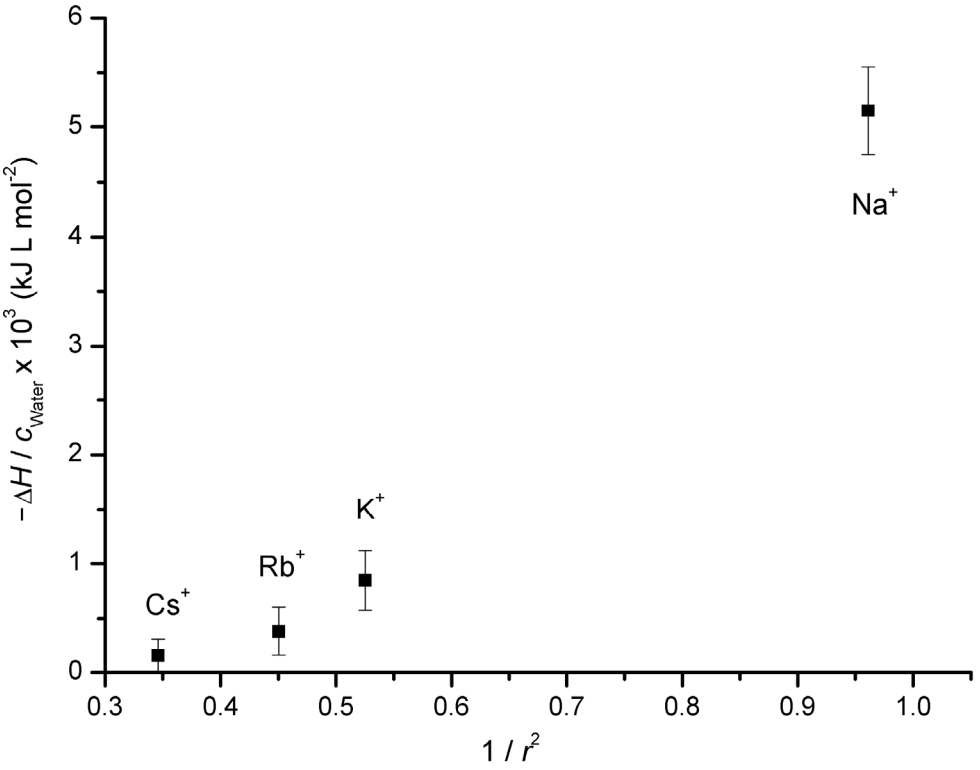


Figure 37: Dependence of interaction magnitude on the cation radius in the reaction between 18C6 and dibenzyldithiocarbamate salts of cations in chloroform and different concentrations of water at $T = 298.15$ K.

A linear dependence of the reaction enthalpy for the complex formation between 18C6 and alkali cations in chloroform in the presence of water on the cation radius suggests a predominant ion-dipole interaction.

4.5 Influence of added methanol on the complexation of crown ethers with cations in chloroform

For a deeper insight into the water effect on the reaction enthalpy in the ligand – cation complexation presented in Section 4.4 and, particularly, if it persists in the case of less polar solvents, a second run of experiments was carried out by replacing water by methanol (see Section 7.4.5).

The data on the influence of methanol on the reaction enthalpy of the complex formation between 18C6 and dibenzyldithiocarbamate salts of Na^+, K^+, Rb^+, and Cs^+ in chloroform are presented in Table 17 and plotted in Figure 38.

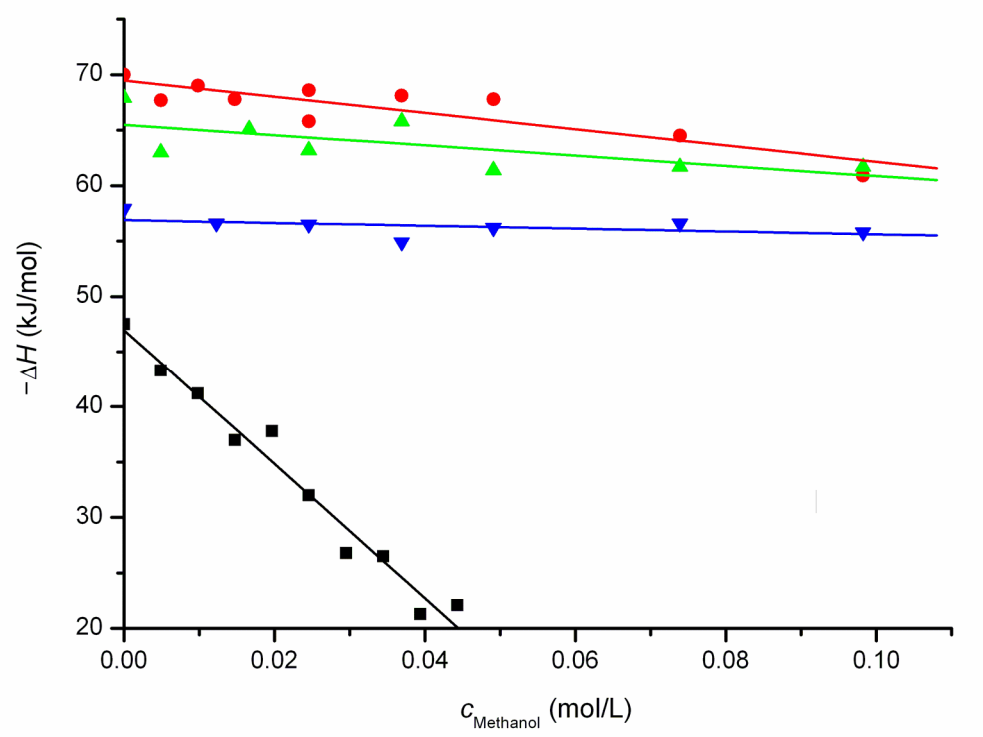


Figure 38: Influence of methanol on the reaction enthalpy for complex formation between 18C6 ($c = 0.02$ mol/L) and dibenzyldithiocarbamate salts ($c = 0.0018$ mol/L): Na^+ (—■—), K^+ (—●—), Rb^+ (—▲—), Cs^+ (—▼—), in chloroform at $T = 298.15$ K.

It was reported that the stability of the complex 18C6:K^+ is higher in methanol than in water, meaning that interactions in 18C6:H_2O are comparatively stronger [238]. The plot of complex interaction magnitude as a function of the cation radius in the reactions between 18C6 and the dibenzyldithiocarbamate salts of cations in chloroform in the presence of methanol suggest that the nature of interactions is not preponderantly electrostatic due to a deviation from the straight line. This is in contrast with the results obtained for the complex formation between 18C6 and alkali cations in chloroform in the presence of water where the interactions are mostly of electrostatic nature.

Table 17: Reaction enthalpy ΔH (kJ/mol) for complex formation of 18C6 with dibenzyldithiocarbamate salts ($c = 0.0018$ mol/L) at different concentrations of methanol in chloroform at $T = 298.15$ K.

Cation	c_{Methanol} (mol/L)	$-\Delta H$	$c_{\text{cation}} : c_{\text{Methanol}}$
Na^+	0.0000	47.5 ± 0.0	1:0.0
	0.0049	43.3 ± 1.2	1:2.4
	0.0098	41.2 ± 1.0	1:4.8
	0.0147	37.0 ± 1.3	1:7.1
	0.0196	34.8 ± 1.2	1:9.3
	0.0246	32.0 ± 0.9	1:12.0
	0.0295	26.8 ± 1.5	1:14.0
	0.0344	26.5 ± 0.7	1:16.0
	0.0394	23.9 ± 0.8	1:19.4
	0.0443	21.3 ± 1.1	1:22.1
	0.0492	22.1 ± 1.4	1:24.3
K^+	0.0000	70.9 ± 1.2	1:0.0
	0.0049	67.7 ± 2.5	1:2.7
	0.0098	69.0 ± 1.8	1:5.3
	0.0147	67.8 ± 2.2	1:8.1
	0.0246	67.2 ± 1.5	1:13.4
	0.0369	68.1 ± 2.3	1:20.1
	0.0491	67.8 ± 2.0	1:26.3
	0.0739	64.5 ± 1.4	1:40.0
	0.0982	60.9 ± 2.5	1:53.5
Rb^+	0.0000	67.9 ± 1.4	1:0.0
	0.0049	63.1 ± 3.5	1:2.7
	0.0166	65.1 ± 2.6	1:8.9
	0.0245	63.2 ± 2.1	1:13.2
	0.0369	65.8 ± 2.8	1:19.9
	0.0491	61.4 ± 2.5	1:26.7
	0.0739	61.7 ± 2.2	1:40.4
	0.0982	61.5 ± 2.0	1:53.4
Cs^+	0.0000	57.9 ± 1.4	1:0.0
	0.0123	56.6 ± 1.2	1:6.6
	0.0245	56.5 ± 0.8	1:13.9
	0.0369	54.9 ± 1.1	1:20.2
	0.0491	56.2 ± 1.5	1:26.7
	0.0739	56.6 ± 0.9	1:39.2
	0.0982	55.8 ± 0.7	1:53.5

Similarly to the results with added water, a correlation is obvious between the cation radii and the influence of methanol on complex formation between 18C6 and alkali metal dibenzyldithiocarbamate salts in chloroform at $T = 298.15$ (Figure 39), however, the influence is much weaker.

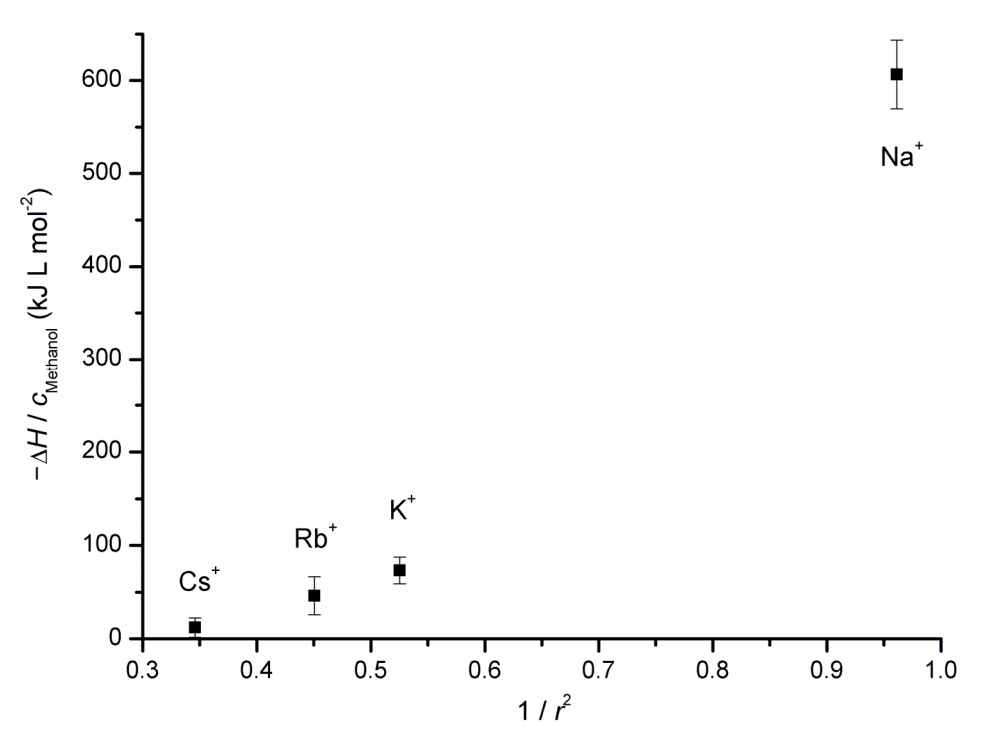


Figure 39: Dependence of interaction magnitude on the cation radius in the reaction between 18C6 and alkali metal cations in chloroform and different concentrations of methanol at $T = 298.15$ K.

In Table 18, the data used in calculations and the measured values determined from experimental plots are presented for the complex formation between 18C6 and dibenzyldithiocarbamate salts of cations in chloroform in the presence of water and methanol, respectively, at $T = 298.15$ K. The hydration of the alkali ions has been studied in chloroform and the values obtained differ from the values obtained for the hydration of the alkali metal ions in gas phase (Table 18) [239].

Table 18: Dependence of the strength of linear correlation between the hydration enthalpy for the complex formation between 18C6 and dibenzyldithiocarbamate salts of cations in chloroform in the presence of water and methanol, respectively, at $T = 298.15$ K, on the cation radius.

Cation	***Radius*** (Å)[a]	$-\Delta H / c_{Water}$ (kJ L mol^{-2})	$-\Delta H / c_{Methanol}$ (kJ L mol^{-2})
Na^+	1.02	5150 ± 702.5	606.5 ± 37.1
K^+	1.38	848.0 ± 71.9	73.3 ± 14.2
Rb^+	1.52	379.3 ± 35.3	46.2 ± 20.4
Cs^+	1.67	152.6 ± 26.9	12.0 ± 10.3

[a] From Ref. [184]

4.6 Influence of acetone and acetonitrile on the complexation of crown ethers with cations in chloroform

The values of reaction enthalpy, ΔH (kJ/mol), for complex formation between 18C6 with sodium dibenzyldithiocarbamate in chloroform and different concentrations of acetone are displayed in Figure 40. The influence of acetone on the reaction enthalpy for the complex formation between 18C6 with sodium salt in chloroform is studied by adding different concentrations of acetone ($0.0-0.1$ mol/L) into reaction medium.

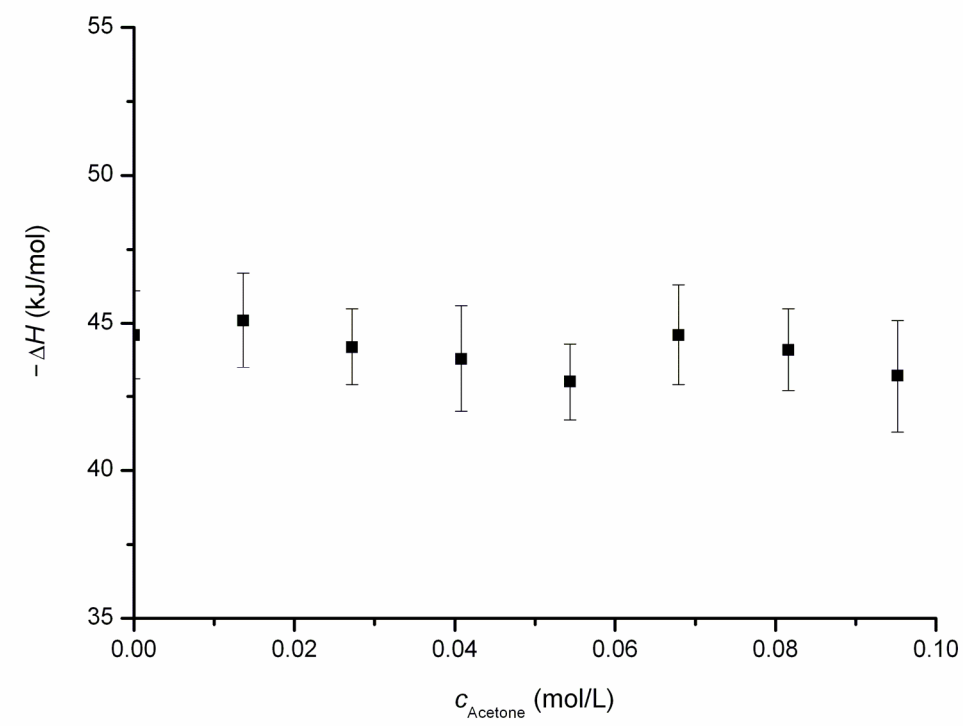


Figure 40: Enthalpy ΔH (kJ/mol) of complex formation between 18C6 ($c = 4.0\times10^{-2}$ mol/L) and sodium dibenzyldithiocarbamate ($c = 2.0\times10^{-3}$ mol/L) in chloroform at various concentrations of acetone.

The value of reaction enthalpy for the complex formation between 18C6 and sodium dibenzyldithiocarbamate in chloroform is not influenced by adding of different concentrations of acetone.

The similar influence upon reaction enthalpy for complex formation of 18C8 with K^+ ($\Delta H = -70.9 \pm 1.7$ kJ/mol), Rb^+ ($\Delta H = -67.9 \pm 1.9$ kJ/mol), and Cs^+ ($\Delta H = -57.9 \pm 2.0$ kJ/mol) dibenzyldithiocarbamate salts in chloroform at different concentrations of acetone ($0.0-0.10$ mol/L) has been observed. To conclude with, the variability in the values of the reaction enthalpy, ΔH, is very small or within the experimental errors for the cations studied.

The influence of the aprotic solvent acetonitrile upon complex formation between 18C6 and alkali metal cation in chloroform has been studied. Similarly with the experiments performed for investigating the influence of acetone over complex formation of 18C6 with alkali cations in chloroform the concentration of acetonitrile has been in the range $0.0-0.12$ mol/L. In Table 19, the results obtained for reaction enthalpy of 18C6 complex formation with sodium

dibenzyldithiocarbamate in chloroform at various concentrations of acetonitrile at $T = 298.15$ K by calorimetric titration are listed.

The value of ΔH for complex formation between 18C6 and sodium dibenzyldithiocarbamate in chloroform is not influenced by added acetonitrile.

Table 19: Reaction enthalpy ΔH (kJ/mol) for complex formation of 18C6 ($c = 0.02$ mol/L) with Na^+-dibenzyldithiocarbamate ($c = 0.002$ mol/L) at various concentrations of acetonitrile (in mol/L) in chloroform at $T = 298.15$ K.

$C_{acetonitrile}$	$-\Delta H$	$c_{Na^+} : c_{CH_3CN}$
0	47.5 ± 1.2	1:0.0
0.019	49.3 ± 1.5	1:9.5
0.038	48.2 ± 1.1	1:18.3
0.077	47.6 ± 1.2	1:36.4
0.115	47.2 ± 1.0	1:57.3

The values of ΔH for the complex formation of 18C6 with potassium dibenzyldithiocarbamate in chloroform and different concentrations of acetonitrile at 298.15 K by calorimetric titrations are given in Table 20.

Table 20: Reaction enthalpy ΔH (kJ/mol) for complex formation of 18C6 ($c = 0.04$ mol/L) with K^+-dibenzyldithiocarbamate ($c = 0.002$ mol/L) at various concentrations of acetonitrile (in mol/L) in chloroform at $T = 298.15$ K.

$C_{acetonitrile}$	$-\Delta H$	$c_{K^+} : c_{CH_3CN}$
0	70.9 ± 1.5	1:0.0
0.004	69.3 ± 1.2	1:1.8
0.019	69.7 ± 1.8	1:9.3
0.039	69.4 ± 1.6	1:19.4
0.057	71.8 ± 2.1	1:28.2
0.077	71.3 ± 1.9	1:35.8
0.115	69.5 ± 1.7	1:57.8

From the data listed in Table 20, it can be seen that the variation of reaction enthalpy is within the experimental errors. The values of ΔH encompass the range from $\Delta H = -69.4$ to $\Delta H = -71.8$. Hence, there is no evidence for any influence of acetonitrile on the complex formation between 18C6 and potassium salt in chloroform under experimental conditions.

In Table 21 the values of reaction enthalpy for the complex formation between 18C6 and rubidium dibenzyldithiocarbamate in chloroform in the presence of various amounts of acetonitrile have been summarized. As can be seen from the data, the presence of acetonitrile does not influence the value of ΔH .

Table 21: Reaction enthalpy ΔH (kJ/mol) for complex formation of 18C6 ($c = 0.02$ mol/L) with Rb^+-dibenzyldithiocarbamate ($c = 0.002$ mol/L) at different concentrations of acetonitrile (in mol/L) in chloroform at $T = 298.15$ K.

$c_{\text{Acetonitrile}}$	$-\Delta H$	$c_{Rb^+} : c_{CH_3CN}$
0	66.1 ± 1.5	1:0
0.009	65.8 ± 2.1	1:4.5
0.019	66.1 ± 1.8	1:9.9
0.029	66.2 ± 2.0	1:13.9
0.038	65.4 ± 1.6	1:18.9
0.048	66.0 ± 2.1	1:23.3
0.057	65.5 ± 1.9	1:30.6
0.067	64.5 ± 1.6	1:32.2
0.077	68.4 ± 2.4	1:39.1
0.086	63.6 ± 2.6	1:42.2
0.115	67.5 ± 2.2	1:58.8

The same situation has been observed for the reaction enthalpy.of complex formation between 18C6 and cesium dibenzyldithiocarbamate in chloroform in the presence of different concentrations of acetonitrile. The results are presented in Table 22.

Table 22: Reaction enthalpy ΔH (kJ/mol) for complex formation of 18C6 ($c = 0.04$ mol/L) with Cs^+-dibenzyldithiocarbamate ($c = 0.002$ mol/L) at different concentrations of acetonitrile (in mol/L) in chloroform at $T = 298.15$ K.

$c_{\text{Acetonitrile}}$	$-\Delta H$	$c_{Cs^+} : c_{CH_3CN}$
0	58.0 ± 0.7	1:0
0.021	57.3 ± 1.5	1:9.9
0.038	58.2 ± 1.3	1:18.9
0.077	56.6 ± 1.4	1:39.1
0.115	59.2 ± 1.0	1:58.8

To conclude with, the reaction enthalpy of the complex formation between 18C6 with alkali metal cations in chloroform is not influenced by the presence of different concentrations of acetonitrile.

4.7 Conclusion - Polar solvent influence upon crown ether and cryptand complexes

The results of the present study reveal that a 1:1 complex formation between 18C6 and water in chloroform occurs. The hydrogen bonding and dipole-dipole interactions are responsible for the complex formation between water molecules and the donor center of the 18C6 macroring.

The values obtained for the reaction enthalpies for complex formation between 18C6 and water in chloroform at different concentrations of water depend on the water concentration, and they are not influenced by the use of various concentrations of 18C6 (see Figure 31).

The values of ΔH of the complex formation between 12C4, 15C5, and B18C6 with water in chloroform showed a trend to decrease along with a decrease in the ring size of the crown ether. Even though 18C6 and B18C6 have similar dimensions of their cavity, the value of reaction enthalpy for the complex formation between B18C6 and water is smaller than those obtained in the reaction of 18C6 and water. This effect is attributed to the benzo substitution in the macrocyclic ring of 18C6, which reduces the basicity of the oxygen atoms attached to the benzo group and the flexibility of the crown ether. As a result, the magnitude of the interaction is reduced.

In order to get more information about the influence of the reaction medium on the complexation between 18C6 and water, the chloroform was replaced by the following halogenated solvents: dichloromethane, 1,2-dichloroethane, and carbon tetrachloride. For the reaction of 18C6 with water in all the mentioned above halogenated solvents, the reaction enthalpy of complex formation between 18C6 with water decreases like carbon tetrachloride > dichloromethane > 1,2-dichloroethane.

The enthalpy for the complex formation between 18C6 with less polar solvents than water, such as methanol, acetone, and acetonitrile in chloroform at 298.15 K for concentrations of the polar solvents within the range $[0.0 - 0.1]$ mol/L have been determined.

The reaction enthalpy ΔH remains constant for methanol concentrations within the range $[0.0 - 0.1]$ mol/L, whereas a significant change occurs at concentrations higher than 0.1 mol/L. For the plateau, where there is no significant change in the reaction enthalpy for the complex formation between 18C6 and methanol in chloroform due to methanol concentration, the existence of a homogeneous mixture between the complex of 18C6 with methanol and chloroform is likely. A possible explanation for the increase in the reaction enthalpy at higher values of methanol concentration resides in the formation of small methanol clusters in the form of aggregates within chloroform. If this is true, it may constitute the framework of studying the solvation of 18C6 in methanol.

In the case of acetone and acetonitrile, there are no significant values of reaction enthalpy for the complex formation of 18C6 with acetone and acetonitrile, respectively, in chloroform.

A linear dependence of the reaction enthalpy for complex formation between 18C6 and alkali metal cations in chloroform in the presence of water on the cation radius suggests a predominant ion-dipole interaction. Also, the results clearly show that the complex formation between NH_4^+ cation with 18C6 in chloroform is not influenced by the presence of water.

The influence of methanol on the complex formation between 18C6 and alkali metal cations in chloroform is weaker than that of water (see Figure 39).

The plot of the complex interaction magnitude as a function of the cation radius in the reaction between 18C6 and alkali metal cations in chloroform in the presence of methanol suggests that the nature of interactions is not preponderantly electrostatic due to a deviation from a straight line.

The hydration of the alkali ions in chloroform differs from the values obtained for the hydration of the alkali ions in gas phase.

The variation in the values of the reaction enthalpy ΔH is very small or within the experimental error for the complex formation of 18C6 with Na^+, K^+, Rb^+, and Cs^+ dibenzyldithiocarbamate salts in chloroform at different concentrations of acetone ($0.0 - 0.10$ mol/L).

The reaction enthalpy of the complex formation between 18C6 and alkali metal cations in chloroform is not influenced by the presence of various concentrations of acetonitrile.

5 Complex formation between Crown Ether Derivatives and Cations in Nonpolar Medium

5.1 Introduction

In Chapter 3 and Chapter 4, the complex formation between crown ethers and [2.2.2] cryptand with alkali metal cations and ammounium ion in nonpolar medium has been studied using calorimetric titrations. By means of host molecules, which absorb in the UV-visible region, spectrophotometric measurements can be employed to obtain the stability constant of a host-guest complex. In this respect, the complex formation between ligands with chromogenic properties as hosts and alkali metal cations as guests in chloroform has been investigated by means of UV-Vis measurements.

The design of new chemical compounds with desirable characteristics is of current interest in chemistry and, especially, in supramolecular chemistry [1, 13]. Several studies have been focused on the design and synthesis of a great variety of functionalized macrocycles like crown ethers, aza crown ethers, cryptands, calixarenes, and cucurbiturils, which are able to recognize and/or exibit catalytic activities on a large area of compounds. Crown ether moieties present in the structure of compounds enforce their known physico-chemical properties and typical application characteristics [20]. Improvements of structures through changing the diameter and the height of the cavity or converting its polarity from hydrophilic into hydrophobic lead to tune the recognition of these materials towards different analytes. There are miscellaneous synthesis strategies based on anchoring crown ether moieties on various molecules [240, 241] in such a way that the whole assembly exhibit directed physico-chemical properties.

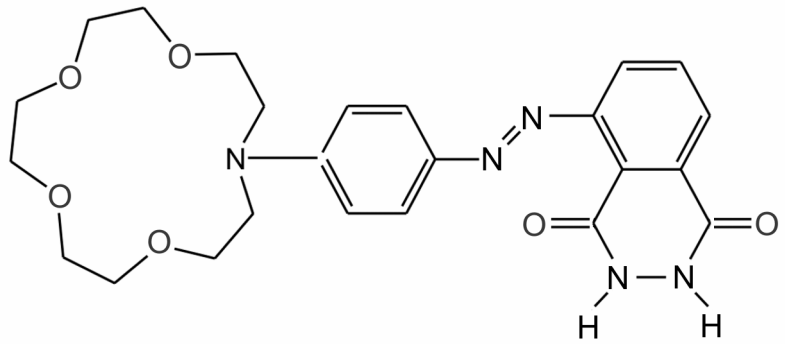


Figure 41: Ligand $\mathbf{L_1}$: 3-[4-(1-aza-15-crown-5)-phenylazo]phthalhydrazide [242].

The ligand $\mathbf{L_1}$ 3-[4-(1-aza-15-crown-5)-phenylazo]phthalhydrazide (Figure 41) which contains the aza-15-crown-5 moiety, is structurally similar to a series of known colorants, namely, the azodyes. The chromogenic properties of the $\mathbf{L_1}$ confer interesting analytical applications [1c]. The ability of $\mathbf{L_1}$ to act as host for complex formation with alkali metal cations as guests in chloroform has been studied by means of UV-Vis measurements.

5.2 Results and Discussion

The red-brick coloured ligand **L_1** is insoluble in water but soluble in organic solvents such as chloroform, dichloromethane, 1,2-dichloroethane, and methanol [242]. Based on the chromogenic properties of this ligand, the complex formation of **L_1** with alkali metal cations in chloroform has been carried out by means of UV-Vis measurements (see Section 7.4.6).

Figures 42 – 46 display the absorption spectra of the complexes formed from **L_1** ($1.84\times10^{-5} - 2.01\times10^{-5}$ mol/L) with alkali metal dibenzyldithiocarbamates in chloroform at different salt concentrations specified in the caption of the above mentioned figures.

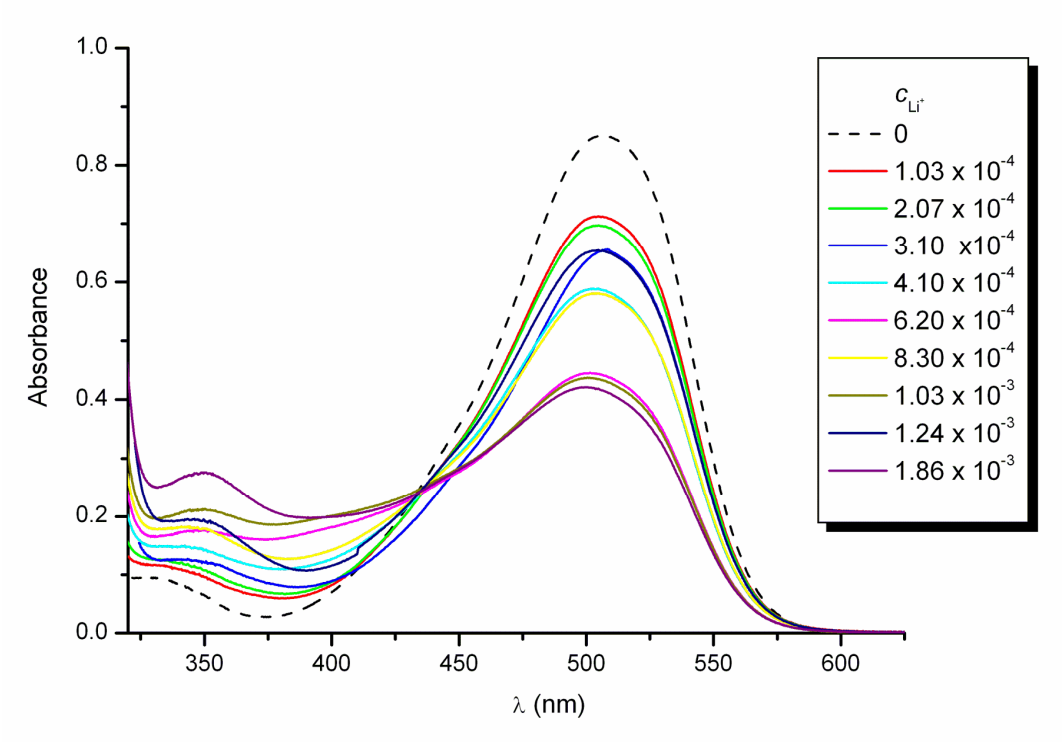


Figure 42: Absorption spectra of the complex formed between **L_1** ($c_{L_1} = 1.84\times10^{-5}$ mol/L) and Li^+-dibenzyldithiocarbamate in chloroform at different salt concentrations (in mol/L); $\lambda_{max} = 505.7$ nm.

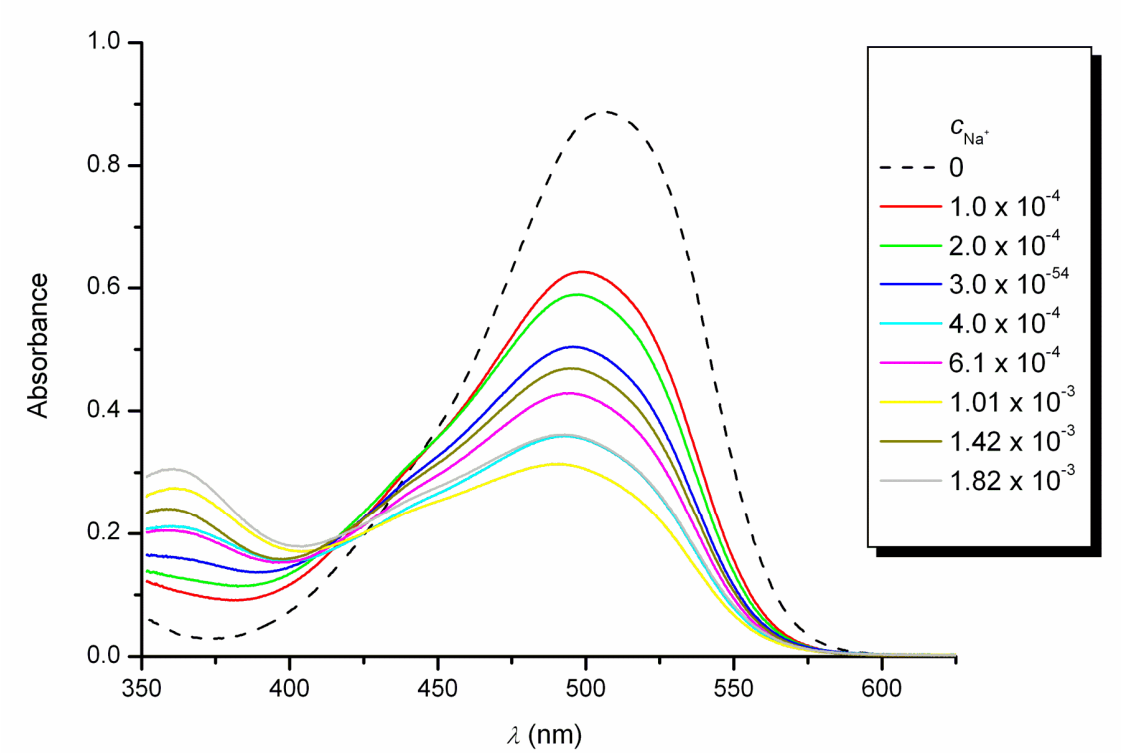


Figure 43: Absorption spectra of the complex formed between $\mathbf{L_1}$ ($c_{L_1} = 2.01\times10^{-5}$ mol/L) and Na^+-dibenzyldithiocarbamate in chloroform at different salt concentrations (in mol/L); $\lambda_{max} = 505.9$ nm and $A_{max} = 0.88728$.

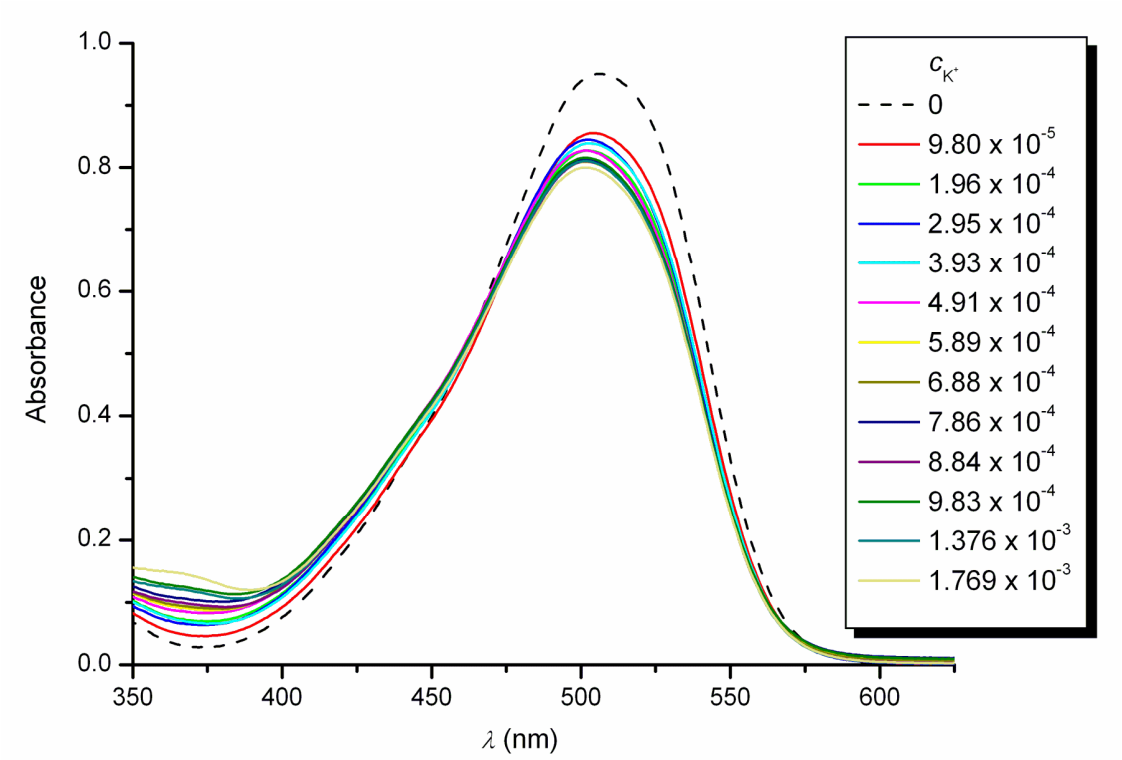


Figure 44: Absorption spectra of the complex formed between $\mathbf{L_1}$ ($c_{L_1} = 2.01\times10^{-5}$ mol/L) and K^+-dibenzyldithiocarbamate in chloroform at different salt concentrations (in mol/L); $\lambda_{max} = 505.6$ nm and $A_{max} = 0.95075$.

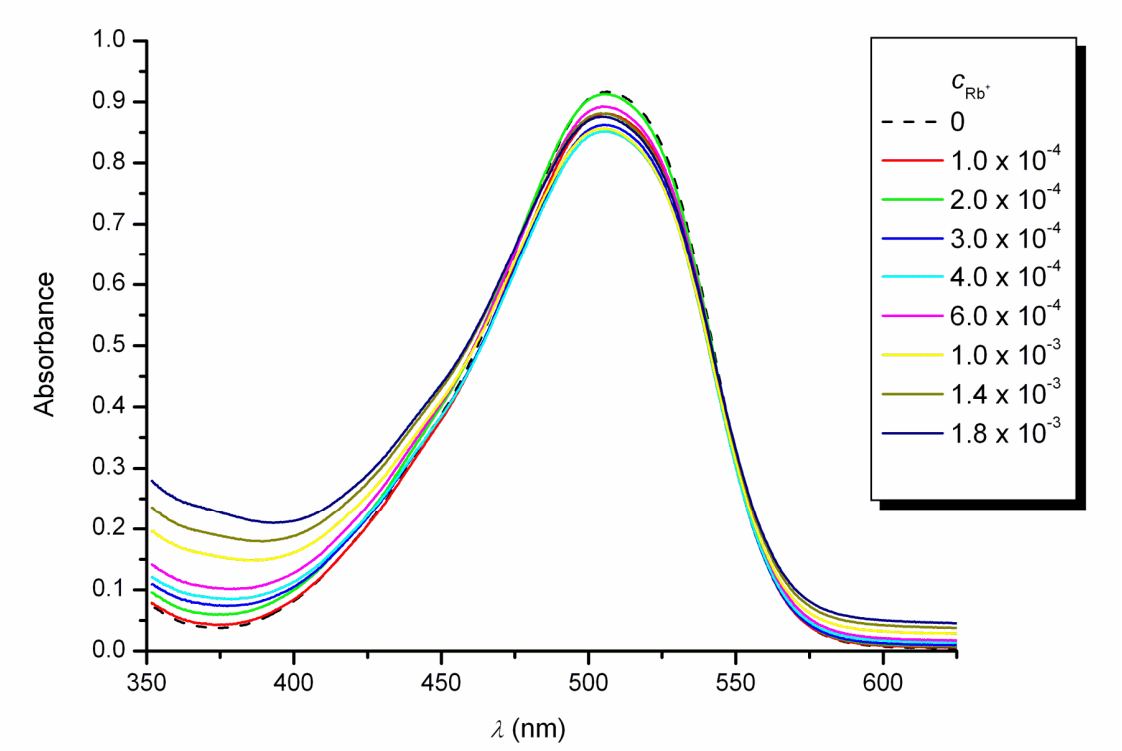


Figure 45: Absorption spectra of the complex formed between $\mathbf{L_1}$ ($c_{L_1} = 2.01\times10^{-5}$ mol/L) and Rb^+-dibenzyldithiocarbamate in chloroform at different salt concentrations (in mol/L); $\lambda_{max} = 506.4$ nm and $A_{max} = 0.91667$.

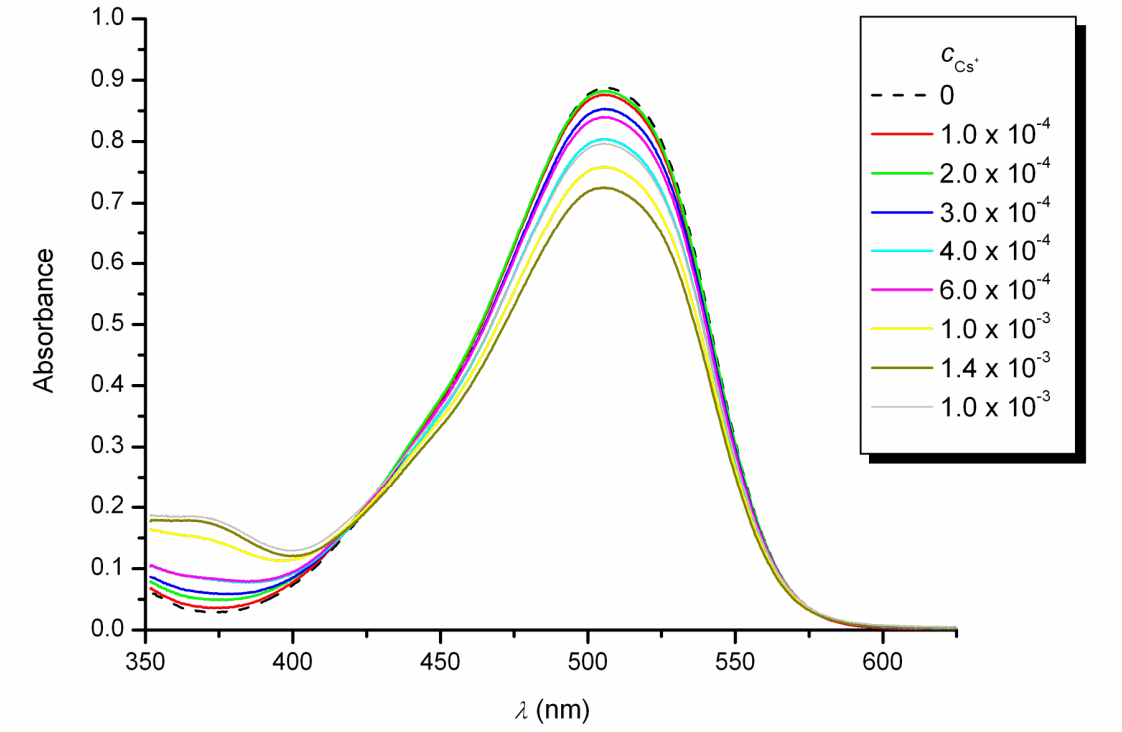


Figure 46: Absorption spectra of the complex formed between $\mathbf{L_1}$ ($c_L = 2.01\times10^{-5}$ mol/L) and Cs^+-dibenzyldithiocarbamate in chloroform at different salt concentrations (in mol/L); $\lambda = 505.7$ nm and $A_{max} = 0.88746$.

The host properties of the ligand **L_1** towards alkali-metal cations (Li^+, Na^+, K^+, Rb^+, and Cs^+) as dibenzyldithiocarbamate salts in chloroform have been investigated. The stability constant of the complexes have been determined on the basis of the spectral changes of the ligand in the presence of variable concentration of alkali metal cations in chloroform. Thus, the stability constants of the complex formation between the ligand **L_1** and cations mentioned above were determined by means of UV-Vis spectrophotometric measurements in chloroform at $T = 298.15$ K.

In Table 23, the values of the stability constants obtained for the complexes are specified. The stability constants for 1:1 complex formation were calculated in according with the procedure presented in eqs. 1.62 – 1.68 discussed in section 1.7.3.2.

Table 23: Logarithmized stability constants Log K (K in L/mol) for the complex formation of **L_1** with alkali metal cations as dibenzyldithiocarbamates salts in chloroform at $T = 298.15$ K.

Cation	***Radius*** (Å)[a]	Log K
Li^+	0.76	3.38 ± 0.01
Na^+	1.02	3.88 ± 0.03
K^+	1.38	4.23 ± 0.01
Rb^+	1.52	4.23 ± 0.02
Cs^+	1.67	4.22 ± 0.01

[a]From Ref. [184]

Following the results presented in Table 23, the values of the stability constants of complexes of alkali metal cations with **L_1** encompass the range from 3.38 (Li^+) to 4.23 (K^+ and Rb^+). It is also worthy to note that the values of the stability constants of the so-formed complexes increase along with the values of the cations' radii.

The stabilities of the complexes formed between **L_1** with K^+, Rb^+, and Cs^+ are similar. To conclude with, this ligand is not able to discriminate the cations mentioned above, although their values of the stability constant are relatively high. Instead, differences appear in the case of complexes formed between **L_1** and Li^+ ($\log K = 3.38$) and Na^+ ($\log K = 3.88$). The decrease in stability of cation complexation with **L_1** follows the sequence: $K^+ \approx Rb^+ \geq Cs^+ > Na^+ > Li^+$.

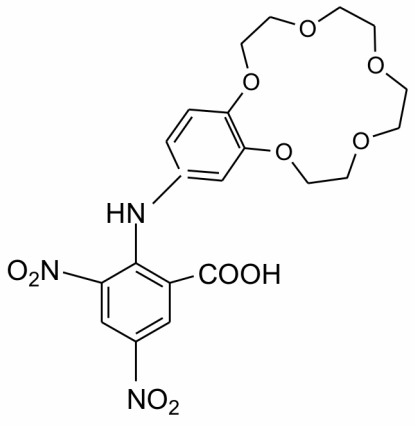


Figure 47: The chemical structure of the ligand **L_2**.

The ability of ligand **L_2,** N(benzo-15-crown-5)-3,5-dinitroanthranilic acid (Figure 47) to form complexes with alkali metal cations as dibenzyldithiocarbamates salts in chloroform was investigated by means of UV-Vis spectrophotometric measurements.

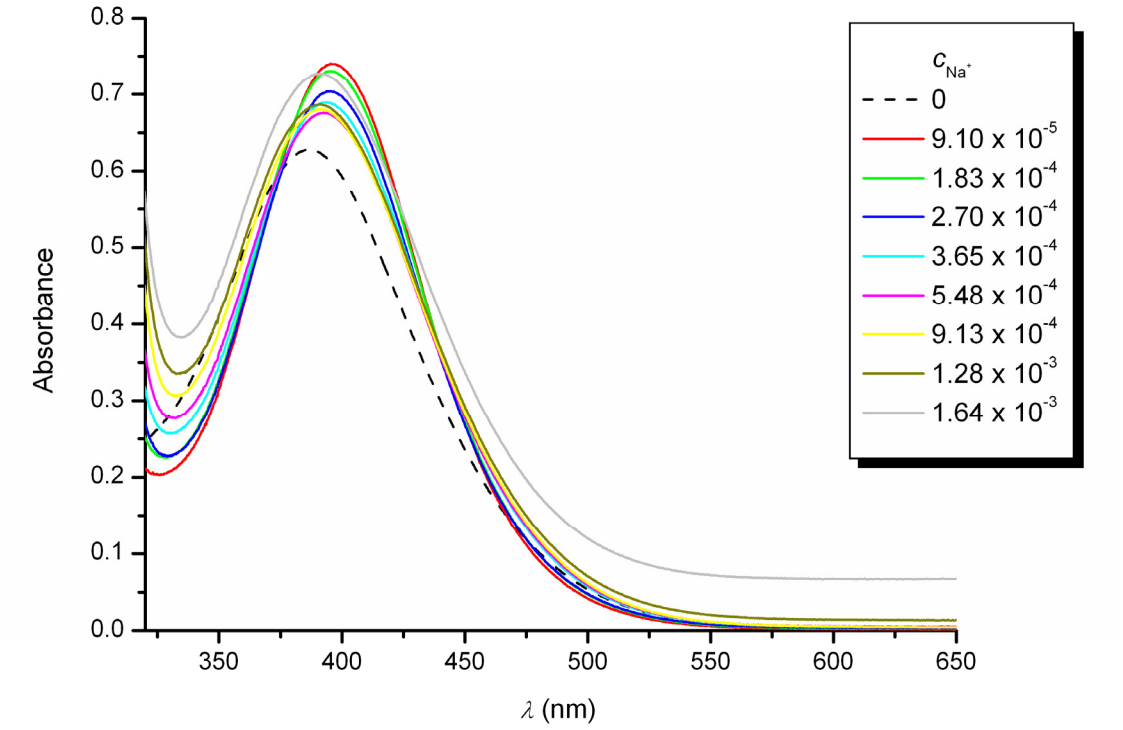


Figure 48: Absorption spectra of the complex formed between **L_2** ($c_{L_2} = 4.42 \times 10^{-5}$ mol/L) and Na+-dibenzyldithiocarbamate in chloroform at different salt concentrations (in mol/L); $\lambda_{max\,L_2} = 387$ nm and $\lambda_{max\,complex} = 387 - 400$ nm.

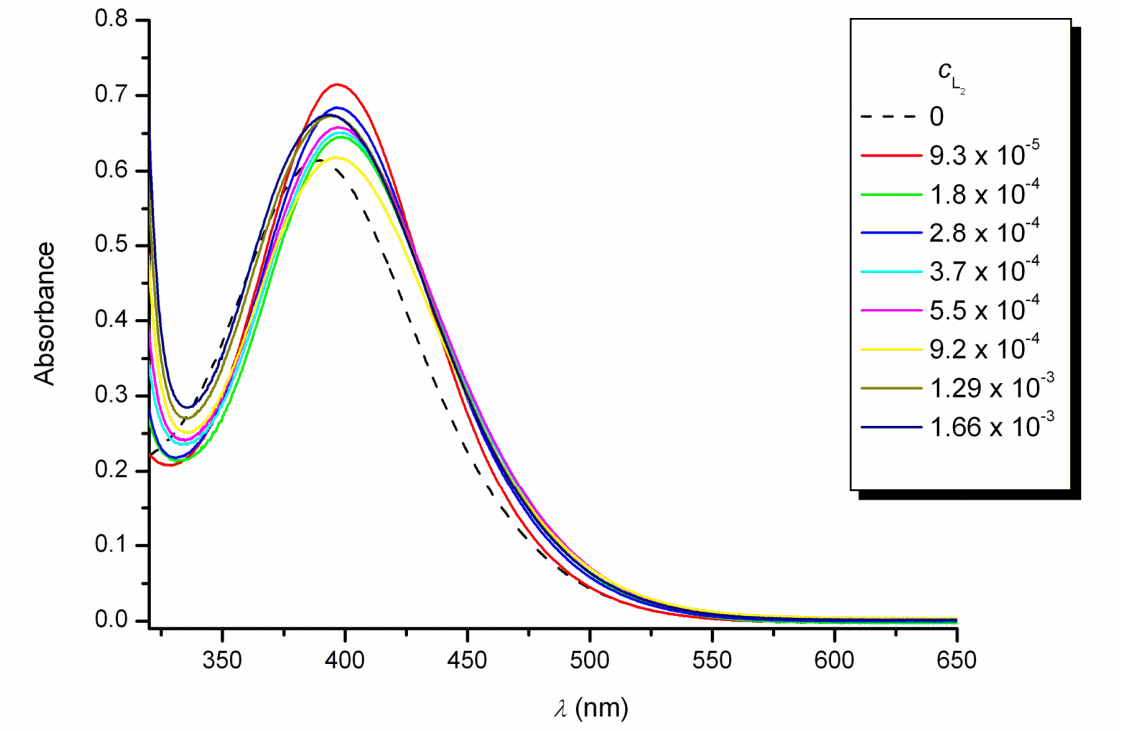


Figure 49: Absorption spectra of the complex formed between **L_2** ($c_{L_2} = 4.42 \times 10^{-5}$ mol/L) and K^+-dibenzyldithiocarbamate in chloroform at different salt concentrations (in mol/L); $\lambda_{max\,L_2} = 387$ nm and $\lambda_{max\ complex} = 387 - 410$ nm.

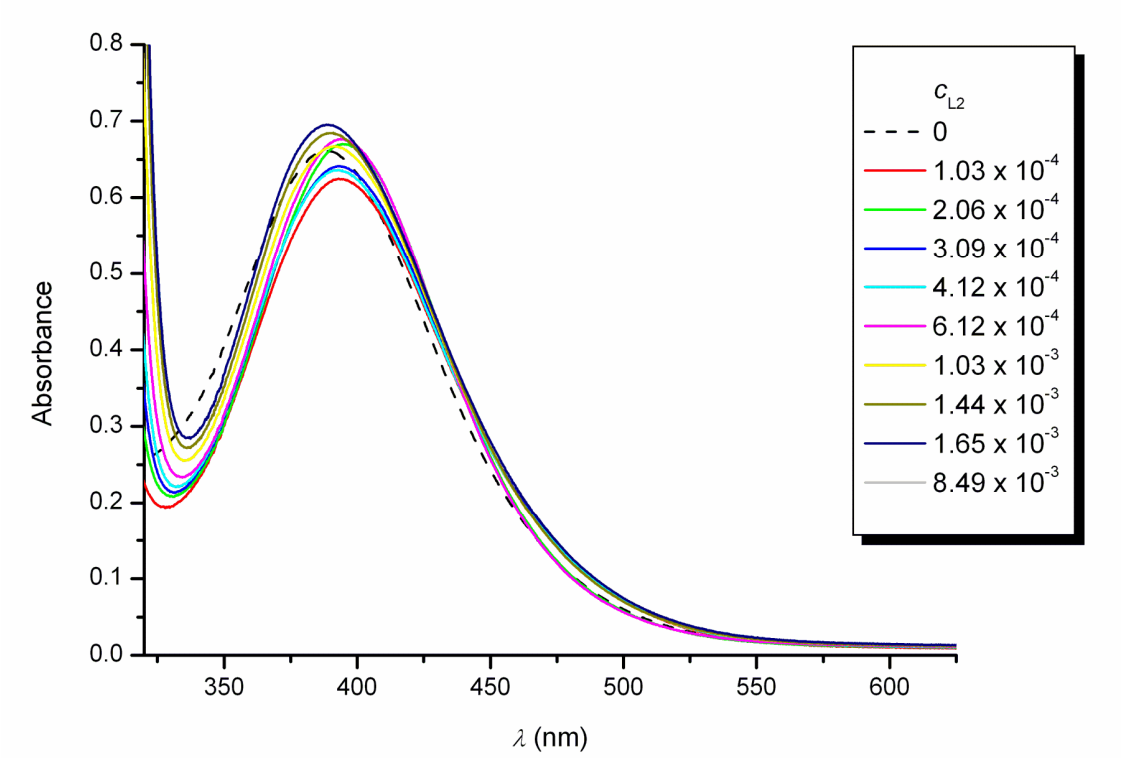


Figure 50: Absorption spectra of the complex formed between **L₂** ($c_{L_2} = 4.37 \times 10^{-5}$ mol/L) and Cs^+-dibenzyldithiocarbamate in chloroform at different salt concentrations (in mol/L) as specified; $\lambda_{max\,L_2} = 387$ nm, $\lambda_{max\ complex} = 387 - 394$ nm.

Figures 48 – 50 display the absorption spectra of complexes formed between **L₂** ($4.37 \times 10^{-5} - 4.42 \times 10^{-5}$ mol/L) and alkali metal cations Na^+, K^+, and Cs^+ as dibenzyldithiocarbamate salts. The λ_{max} of the complex formed from the ligand and alkali metal ions is shifted towards higher wavelengths (bathochromatic effect) as compared with the absorption of the free ligand ($\lambda_{max\,L_2} = 387$ nm).

The logarithmized values of the stability constants for the complex formation of **L₂** with Li^+, Na^+, K^+, Rb^+, and Cs^+ cations in chloroform are shown in Table 24.

Table 24: Logarithmized stability constants Log *K* (*K* in L/mol) for the complex formation of **L₂** with alkali metal cations as dibenzyldithiocarbamates salts in chloroform at $T = 298.15$ K.

Cation	***Radius*** (Å)[a]	Log *K*
Li^+	0.76	4.10 ± 0.01
Na^+	1.02	4.11 ± 0.01
K^+	1.38	4.12 ± 0.01
Rb^+	1.52	4.09 ± 0.02
Cs^+	1.67	4.11 ± 0.01

[a]From Ref. [184]

From the data displayed in Table 24 one can conclude that **L_2** forms complexes with the cations with quite similar stability constants. This ligand does not show selectivity for certain alkali metal cations. Likewise, the results are similar to those obtained by complexation of alkali metal cations with B15C5 using calorimetric titration in chloroform (Chapter 4).

The stability constants of K^+-perchlorate complexes with nearly insoluble ligands L_1, and L_2 are determined in aqueous solution by measuring the increase in solubility of a nearly insoluble ligand due to complex formation with a soluble guest [243]. The solubilities of the ligands **L_1** and **L_2** have been obtained from the measurements of the TOC values as a function of the total salt concentration.

The results are summarized in Table 25. It follows that the solubility of ligands in water increases due to complex formation (see Section 7.4.7).

Table 25: Logarithmized stability constants Log K (K in L/mol) of complex formation between K^+ and L_1 and L_2 in water at $T = 298.15$ K.

Ligand	***Solubility***[a] (mol/L)	Log K
L_1	7.45×10^{-4}	1.7 ± 0.2
L_2	3.60×10^{-3}	1.4 ± 0.2

[a]from TOC

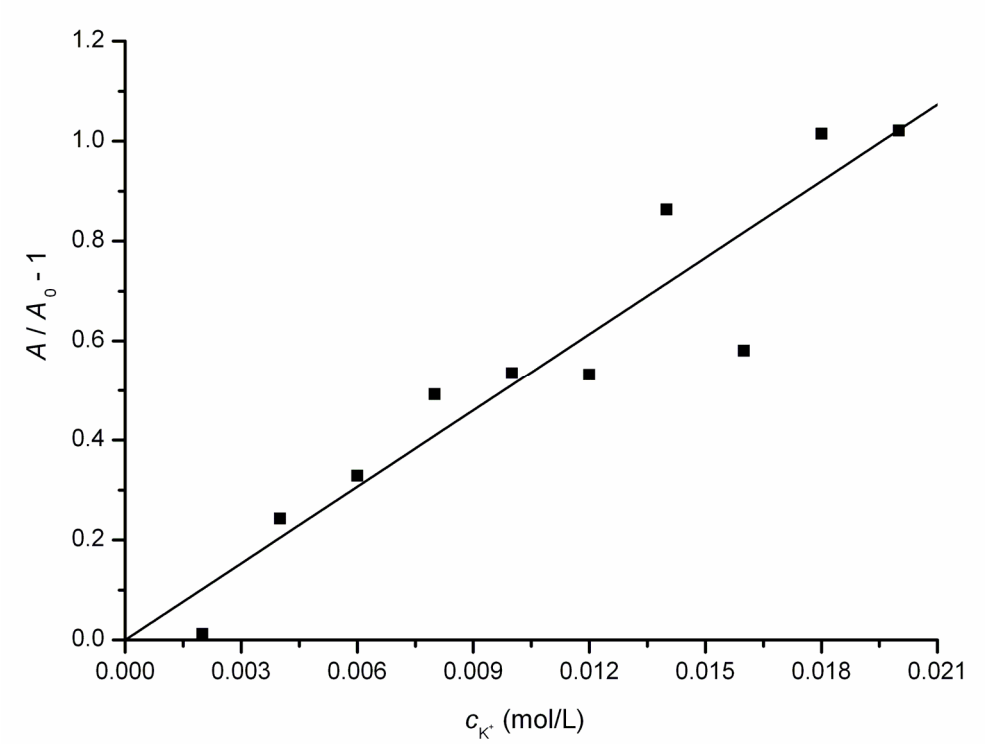


Figure 51: Plot of $A/A_0 - 1$ at $\lambda = 434$ nm of a saturated solution of the ligand **L_1** against the total salt concentration.

In Figure 51, the absorbance of solutions saturated with ligand L_1 are shown as a function of the salt concentration. Due to the complex formation, the total concentration of the ligand in solution increases. By plotting $A/A_0 - 1$ at a constant wavelength as a function of the total salt concentration, one expects a straight line to be found. By linear interpolation of the experimental data, the slope *b* of the line gives the stability constant *K*.

5.3 Conclusion – Complexes of crown ether derivatives with cations

The host properties of the ligand **L_1** towards alkali metal cations, Li^+, Na^+, K^+, Rb^+, and Cs^+ as dibenzyldithiocarbamate salts in chloroform have been studied.

The stability constant of the formed complexes have been determined on the basis of the spectral changes of the ligands in the presence of variable concentration of alkali metal cations in chloroform.

The values of the stability constants of the complex formation between ligand **L_1** and cations are in the range starting from 3.38 (Li^+) to 4.23 (K^+ and Rb^+). The values of the stability constants of the complexes increase along with the values of the cations' radii. The ligand has no selectivity for the following cations: K^+, Rb^+, and Cs^+. In contrast, differences appear in the case of complexes formed between **L_1** and Li^+, as well as between **L_1** and Na^+.

The wavelength corresponding to maximum absorption, λ_{max}, of the complex formed between the ligand **L_2** and alkali metal ions at different concentrations is shifted towards higher wavelengths (i.e., bathochromatic effect) as compared with the absorption of the free ligand ($\lambda_{max\,L_2} = 387$ nm).

The ligand **L_2** forms complexes with the alkali metal cations as dibenzyldithiocarbamate salts in chloroform having quite similar stability constants. Thus, this ligand does not exhibit selectivity for the alkali metal cations.

The solubilities of the ligands **L_1** and **L_2** have been obtained from the measurements of the TOC values as a function of the total salt concentration. The stability constant of the complexation of potassium perchlorate with the nearly insoluble ligands **L_1** and **L_2** in aqueous solution has been determined.

6 Complex formation of cyclodextrins with amides and nitriles

6.1 Introduction

In Chapters 3-5 of the present work, the complex formation between crown ethers and cryptands with charged guest, such as alkali metal or ammonium cations in halogenated organic solvents has been studied. Mainly the ion-dipol interactions together with hydrogen bonds are responsible for the complex formation between host and charged guest molecules. The study proceeds with complex formation between uncharged host and guest molecules such as cyclodextrin with amides and nitriles.

Natural cyclodextrins (α-, ß-, and γ-cyclodextrin) are adequate host molecules for the recognition in aqueous media of various hydrophobic guest molecules [100-105] (Section 1.6). They are characterized by a fairly polar exterior and a nonpolar cavity. Thus, a large number of nonpolar organic molecules can be included into the cavity of cyclodextrins. Cyclodextrins allow forming complexes with organic molecules having polar groups too. These groups are located outside and the nonpolar part of molecule inside the cavity of cyclodextrin. Thus, charged groups such as ammonium and carboxylate, or hydrophilic groups such as hydroxyl, amino, and carboxyl, remain exposed to the bulk solvent after the inclusion of the hydrophobic part of molecule inside the cavity of cyclodextrin [244]. The principal driving forces involved in complexation are weak interactions, such as hydrophobic effects and van der Waals interactions, determined by a combination of various factors [110-115]. Hydrogen bonding is also involved in some complexes. As mentioned in Section 1.6, there are numerous studies dedicated to the experimental techniques used for investigation of inclusion complexes, such as NMR measurements, calorimetric or microcalorimetric titrations, potentiometric titrations, mass spectrometry, and ultrasonic measurements [100, 120-123].

The optimal fit between the guest molecules and the cavity of the cyclodextrins has also a pronounced influence upon the stability of the complexes formed in solution. The hydrophobic interactions are responsible for complex formation between the uncharged host and guest molecules. It is known from crystal structure determinations that α-cyclodextrin forms a hydrate with six water molecules [104]. Thus, four water molecules are located outside and two inside the cavity of α-cyclodextrin. Saenger [245] called the water molecules inside the cavity "high-energy water". These water molecules are not energetically comparable with water molecules from the bulk phase. The release of the water molecules from the cavity should result in favorable enthalpic and entropic contributions to the Gibbs free energy. Studies on the influence of the solvation upon the reaction of α-cyclodextrin with carboxylic acids, their methyl esters, and their sodium salts in aqueous solution by means of calorimetric titration revealed that the complex formation is influenced in the positive direction by the release of "high-energy water" from the cavity of α-cyclodextrin [246]. The reaction enthalpy and entropy for the complex formation increase along with the increase in chain length of the carboxylic acids and their derivatives.

Relevant investigations of inclusion complexes between α-cyclodextrin and aliphatic guest molecules have been carried out and interesting papers have been reported on this issue [247-249]. In this respect, linear long-chain aliphatic compounds bearing amino or carboxylic

functional groups may insert their hydrophobic tail into α-cyclodextrin (the narrowest of the cyclodextrin family) [250, 251].

In this study, we have investigated the complex formation between α-cyclodextrin (Figure 52) and some amides and nitriles in aqueous solution by means of calorimetric titrations.

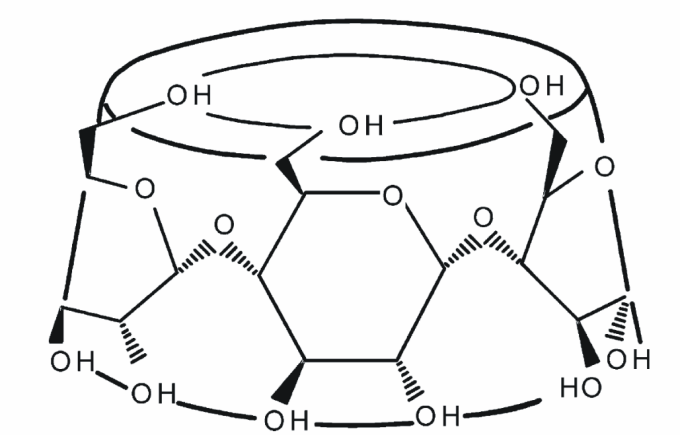


Figure 52: The chemical structure of α-cyclodextrin.

6.2 Results and Discussion

The stability constants and thermodynamic values for complex formation between α-cyclodextrin and amides in aqueous solution are summarized in Table 26 (see Section 7.4.8). Amides are compounds containing the group – $CONH_2$. This type of group is important in proteins. Thus, in protein chains, amino acids are connected by amide bonds.

Table 26: Log K (K in L/mol) and thermodynamic values ΔH (in kJ/mol) and TΔS (in kJ/mol) for the complex formation of α-CD with amides in aqueous solution at 298.15 K.

Amide	*Log K*	*– ΔH*	*TΔS*
CH_3CONH_2 Acetamide	-[a]	< 0.5	-
$CH_3CH_2CONH_2$ Propionamide	-[a]	< 0.5	-
$CH_3CH_2CH_2CONH_2$ *n*-Butyramide	2.54 ± 0.04	0.67 ± 0.12	13.7 ± 0.6
$CH_3CH_2CH_2CH_2CONH_2$ Valeramide	2.67 ± 0.1	5.12 ± 0.10	10.1 ± 0.4
$CH_3CH_2CH_2CH_2CH_2CONH_2$ Hexanamide	2.57 ± 0.03	13.37 ± 0.3	1.2 ± 0.8

[a] Not calculable from thermogram

The values of the stability constants calculated from calorimetric titrations in aqueous solution are nearly identical within the experimental errors. Instead, a slow increase of the values of reaction enthalpies can be noticed along with an increasing number of methylene groups. The values of the reaction entropy decrease with increasing number of methylene groups.

In the case of acetamide (CH_3CONH_2) and propionamide ($CH_3CH_2CONH_2$) any complex formation with α-cyclodextrin can not be achieved. The complex formation between α-cyclodextrin and *n*-butyramide, valeramide, and hexanamide is favored by enthalpic and by entropic contributions. In the case of the cyclodextrins, it is known that in their cavities water molecules are present, which are released upon guest inclusion. The complex formation is favored by release of water molecules from the cavity of α-cyclodextrin.

In Table 27 the stability constants and thermodynamic values for the complex formation between α-cyclodextrin and some nitriles in aqueous solution are presented. Nitriles (compounds containing the cyano group, -CN) are considered to be acid derivatives because they can be hydrolyzed to form amides and carboxylic acids.

Table 27: Logarithmized stability constants log *K* (*K* in L/mol) and thermodynamic values ΔH (kJ/mol) and $T\Delta S$ (kJ/mol) for the complex formation of α-CD with nitriles in aqueous solution at *T*=298.15 K.

Nitrile	Log *K*	$-\Delta H$	$T\Delta S$
CH_3CH_2CN Propionitrile	2.49 ± 0.04	1.86 ± 0.12	12.3 ± 0.8
$CH_3(CH_2)_3CN$ Valeronitrile	2.79 ± 0.09	7.58 ± 0.02	8.3 ± 0.5
$CH_3(CH_2)_6CN$ Caprylonitrile	2.98 ± 0.12	16.90 ± 1.0	0.1 ± 1.6

It was reported that the affinity to α-cyclodextrin steadily increases with increasing alkyl chain length [252]. The data presented in Table 27 indicate a continuous increase of the values of the stability constants from $\log K = 2.49$ for propionitrile to $\log K = 2.98$ for caprylonitrile along with the increase in the length of the alkyl chain. The reaction enthalpy, for the complex formation between α-cyclodextrin with nitriles in aqueous solution also increases with an increasing number of methylene groups while the values of the reaction entropy decrease. The complex formation between α-cyclodextrin with nitriles is favored by enthalpic contributions and by entropic contributions. This effect can be attributed to the liberation of the so called "high-energy water" from the cavity of the α-cyclodextrin molecules.

6.3 Conclusion – Complexes of cyclodextrin with amides and nitriles

Both amides and nitriles under study are able to form complexes with α-cyclodextrin. The values of the stability constants of complex formation between α-cyclodextrin and amides CH_3-$(CH_2)_n$-$CONH_2$ with n > 3 calculated from calorimetric titrations in aqueous solution are nearly identical within the experimental errors. Instead, a slow increase of the values of reaction enthalpies can be noticed with increasing number of methylene groups. The values of the reaction entropy decrease with increasing number of methylene groups.

The values of the stability constants of the complexes formed between α- cyclodextrin and nitriles CH_3-$(CH_2)_n$-CN increase along with increasing number of methylene groups. Increasing values of the reaction enthalpy can be noticed along with an increasing number of methylene groups, while the reaction entropy decreases with the increasing number of methylene groups. The complex formation between α-cyclodextrin and nitriles is favored by enthalpic contributions and by entropic contributions. This effect can be attributed to the release of water molecules from the cavity of the α-cyclodextrin cavity having higher energy than the water molecules in the bulk phase.

The results demonstrate the influence of solvation changes during the complex formation of uncharged molecules with α-cyclodextrin. In this respect, the complex formation of α-cyclodextrin with amides and nitriles is mainly favored by the release of water molecules from the cavity of α-cyclodextrin.

The complex formation between crown ethers and alkali metal cations, where the reaction enthalpy decreses with increasing cation radius and the entropy increases (Chapter 3), is favored by the enthalpic contributions. Instead, the entropic contributions are responsible for the complex formation between the uncharged host and guest molecules, particularly, the complex formation of α-cyclodextrin with amides and nitriles.

7 Experimental Part

7.1 Materials and Apparatus

7.1.1 Chemicals

Ligands

12-crown-4 (1,4,7,10-Tetraoxacyclodecan)	(> 98%, Merck)
15-crown-5 (1,4,10,13-Pentaoxacyclopentadecan)	(> 98%, Merck)
18-crown-6 (1,4,7,10,13,16-Hexaoxacyclooctadecan)	(> 99%, Merck)
Benzo-12-crown-4 (1,4,7,10-Tetraoxa[10]orthocyclophan)	(> 98%, Merck)
Benzo-15-crown-5 (1,4,7,10,13-Pentaoxa[13]orthocyclophan)	(> 98%, Merck)
Benzo-18-crown-6 (1,4,10,13,16-Hexaoxa[16]ortocyclophan	(> 99%, Merck)
Dibenzo-15-crown-5(Dibenzo[b,h]6,7,9,10,17,18-hexahydro-1,4,7,10,13-pentaoxacyclopentadesine	(> 98%, Merck)
Dibenzo-18-crown-6 (1,4,7,14,17,20-Hexaoxa[7.7]orthocyclophan	(> 98%, Merck)
Cryptand [2.2.2](4,7,13,16,21,24-Hexaoxa-1,10-diazabicyclo[8.8.8]hexacosan)	(> 98%, Merck)
α-cyclodextrin	(Pharma-Grade, Wacker)
L_1 3-[4-(1-aza-15-crown-5)-phenylazo]phthalhydrazide	*Dr. Titus Constantinescu*
L_2 N(benzo-15-crown-5)-3,5-dinitroanthranilic acid	*Dr. Titus Constantinescu*

Salts

Barium perchlorate	(puriss.p.a., Merck)
Cesium dibenzyldithiocarbamate	*Radu-Cristian Mutihac*
Litium dibenzyldithiocarbamate	*Radu-Cristian Mutihac*
Potassium dibenzyldithiocarbamate	*Radu-Cristian Mutihac*
Rubidium dibenzyldithiocarbamate	*Radu-Cristian Mutihac*
Sodium dibenzyldithiocarbamate	*Radu-Cristian Mutihac*

Ammonium salts:

Ammonium dibenzyldithiocarbamate	*Radu-Cristian Mutihac*
Ammonium diethyldithiocarbamate	(puriss. p.a., Fluka)
Ammonium perchlorate	(puriss. p.a., Fluka)
Ammonium 1-pyrrolidinedithiocarboxylate	(≥ 98.0 %, Fluka)

Solvents

Acetone	(SupraSolv, Merck)
Acetonitrile	(HPLC Grade, Merck)
Carbon tetrachloride	(≥ 99.8 %, Fluka)
Chloroform	(HPLC Grade, Rathburn)

Dibenzylamine	(≥ 96 %, Merck)
1, 2-Dichloroethane	(≥ 99.5 %, Merck)
Dichloromethane	(≥ 99.9 %, Roth)
1,4-Dioxane	(≥ 99.5 %, Fluka)
Methanol	(HPLC Grade, Roth)
Water	MembraPur, Milli Q

Amides:

Acetamide	(99%, Fluka)
n-Butyramide	(99%, Acros)
Hexanamide	(97%, Acros)
Propionamide	(97%, Acros)
Valeramide	(97%, Acros)

Nitriles:

Caprylonitrile	(97 %, Acros)
Propionitrile	(99 %, Merck)
Valeronitrile	(99.5 %, Aldrich)

7.1.2 Apparatus

Calorimeter

Calorimetric titrations were carried out by means of a Calorimeter "Tronac 450" from *Tronac* Company, Orem, Utah, USA. For the alterations of the thermal signal in dependence on the time recorded a Microvoltmeter of the model "197" of the *Keithley Instruments GmbH* Company, Germering, Germany and a x,y - plotter model "SE 130" of the *ABB Goertz* Company, Mannheim, Germany are used.

UV-Vis Spectrophotometer

Spectrophotometric measurements were carried out by means of a UV-Vis Spectrophotometric Varian "Cary 5E. A UV-Vis spectrum of a compound is obtained by comparing the radiation absorbed by a solution of the compound with the radiation absorbed by a similar thickness of pure solvent.

TOC

The total organic carbon (TOC) content of the solution was measured by means of a "TOC-5050" from *Shimadzu Deutschland GmbH,* Duisburg, Germany.

7.2 Synthesis

7.2.1 Synthesis of dibenzyldithiocarbamte salts

The solubility of dibenzyldithiocarbamates is high enough for calorimetric titrations. The synthesis of different alkali and of the ammonium dibenzyldithiocarbamates follows the known Moore's procedure for the formation of the sodium salt [183]. Instead of sodium hydroxide the corresponding alkali or ammonium hydroxides are used during the synthesis.

In a 250 mL beaker containing 50 mL of acetone 38 mL of dibenzylamine are dissolved. The solution is cooled to below 10°C. A solution of 12 mL of carbondisulfide in 13 mL of acetone is added dropwise while stirring to the cooled solution maintaining a temperature ≤ 10°C. Next, a solution of 4.4 g of sodium hydroxide (0.11 moles) in 20 mL of water is cooled to ≤ 5°C and slowly added to the mixture, while the temperature has to be kept below ≤ 10°C. The reaction mixture is concentrated *in vacuo* by 30-40 mL, then 50 mL of diethyl ether are added, and another fraction of 40-50 ml is removed *in vacuo*. This step has to be repeated at least three times, while the crystallization of the product starts. The crystals are filtered off and washed with diethyl ether several times. By concentrating the combined filtrates and washings, futher crops of crystals may be obtained.

By replacing sodium hydroxide by other hydroxides (e.g. KOH, LiOH, NH_4OH, 0.11 moles for alkali, 0.055 moles for earth alkali hydroxides) dibenzyldithiocarbamates of other metals can be obtained.

Thus, the dibenzyldithiocarbamate salts of lithium, sodium, potassium, rubidium, cesium, and ammonium have been prepared and used in calorimetric titration and UV-Vis measurements.

7.3 Solution preparation

All the solutions of ligands and cations have been prepared by introducing the weighed components into the corresponding solvents used in the measurements. Several salts are dissolved in chloroform. Only the solubility of dibenzyldithiocarbamates is high enough for calorimetric titration. In this respect the synthesis of alkali and of the ammonium dibenzyldithiocarbamate following the procedure described in the Section 7.2.1 has been done.
The solvent chloroform has been dried over a long period by means of molecular sieves (4 Å). All measurements are performed several times using different samples of chloroform to ensure the reproducibility of the results. Acetonitrile, methanol, acetone, dichloromethane, 1,2-dichloroethane, carbone tetrachloride were used in anhydrous quality and dried over molecular sieve (3 and 4 Å) before use. Bidistilled water was used as solvent.

7.4 Methods for the determination of the stability constant and thermodynamic values of the complex formation

Calorimetric titration

During the calorimetric titration a solution of one ligand (0.06 - 0.08 mol/L) is added continuously into 40 mL of a solution containing the guest molecule (3.0 - 6.0 x 10^{-3} mol/L), in the Dewar vessel. The addition of the ligand takes place with known speed over a motor-driven buret so that exact readings about the concentrations of the ligand and the guest compound can be made at every time of the titration in the reaction vessel. By using a Wheatstone bridge the resistance measured by a thermistor as a function temperature alteration of the chemical reaction is correlated.

UV-Vis spectrophotometric measurements

The spectral changes of $\mathbf{L_1}$ solution and $\mathbf{L_2}$ solution (1.84 x 10^{-5} – 2.01 x 10^{-5} mol/L) were recorded upon stepwise addition of an alkali salt solution (1.03 x 10^{-4} – 1.86 x 10^{-3} mol/L). Absorbances were sampled at 1 nm intervals. Titrations for each M^+/L system were repeated three or four times. The obtained spectrophotometric data were processed using the mathematical treatment presented in eqs. 1.62-1.68 from Section 1.7.3.2.

TOC measurements

The solid ligand $\mathbf{L_1}$ and $\mathbf{L_2}$ is added to the solutions containing different concentrations of potassium salts in water. The amount of the solid ligand was high enough to ensure the formation of salt solutions saturated with the ligands. The solutions were stirred for several days. Samples of the solutions were analysed after 3 and 4 days. The solutions were centrifuged and the resulting clear solutions filtered through a membrane filter to remove the undissolved ligands. Afterwards the total organic carbon content of the solution was measured (TOC-5050, Shimadzu). All solutions were thermostated at 298.16 K. The same procedure has been applied in the case of L_2.

7.4.1 Determination of the stability constant and thermodynamic values of the complex formation between 18C6 and barium and ammonium perchlorate in different mixture of water with dioxane

The stability constants and reaction enthalpies for the complexation of the barium cation with 18C6 were measured by means of calorimetric titrations. Solutions of the ligand 18C6 (0.06-0.08 mol/L) were added continuously to solutions of barium perchlorate (4.0-5.0 x 10^{-3}mol/L) in different mixture of water with dioxane. The heat Q produced during titration was related to the reaction enthalpy ΔH after correction for all non-chemical heat effects by the following equation:

$$Q = \Delta n \cdot \Delta H$$

with Δn indicating the number of moles of the complex formed. The mathematical treatment of the experimental data is described in Section 1.7.3 [146, 150, 151]. Each titration has been

repeated at least five times. The accuracy of the calorimeter used is controlled using as standard the reaction between β-cyclodextrin and cyclohexanol (log K = 2.92 ± 0.03 and ΔH = -11.8 ± 0.6 kJ/mol) in aqueous solution. These values agree well with the results reported in the literature (log K = 2.78 ± 0.02 and ΔH = -9.9 ± 0.2 kJ/mol) [108]. The same procedure has been applied for the calorimetric titration of 18C6 (0.06-0.08 mol/L) with ammonium perchlorate ($3.0 - 5.0 \times 10^{-3}$) in different mixture of water with dioxane. The experiments were done at 298.15 K.

7.4.2 Determination of the stability constant and reaction enthalpy and entropy for the complex formation between crown ethers and alkali metal cations in chloroform

During the calorimetric titration a solution of the ligands 12-crown-4, Benzo-12-crown-4, 15-crown-5, Benzo-15-crown-5, Dibenzo-15-crown-5, and 18-crown-6 (0.02-0.04 mol/L) are added continuously to the solution containing the Na^+, K^+, Rb^+, and Cs^+ dibenzyldithiocarbamate salts (0.0018 – 0.002 mol/L) in chloroform.

The mathematical treatment of the experimental data has been described in detail in Section 1.7.3 [146, 150, 151]. Each titration has been repeated at least five times. The accuracy of the calorimeter was controlled using as standard the reaction between 18-crown-6 with $Ba(ClO_4)$ in aqueous solution. The values obtained for the stability constant (log K = 3.55 ± 0.03 and for the reaction enthalpy (ΔH = - 31.7 ± 0.8 kJ/mol) in aqueous solution were in good agreement with the results reported in the literature (log K = 3.50 ± 0.08; ΔH = - 31.5 ± 1.2 kJ/mol) [154]. The calorimetric titrations were performed using a Tronac Model 450 calorimeter. The experiments were done at 298.15 K.

7.4.3 Complex formation of ammonium salts with crown ethers and cryptand [2.2.2] in chloroform at 298.15 K

The complexation enthalpies between ammonium ions such as ammonium dibenzyldithiocarbamate, $(C_6H_5CH_2)_2NC(S)S^-NH_4^+$, ammonium 1-pyrrolidinedithio-carboxylate, $C_4H_8NC(S)S^-NH_4^+$, and ammonium diethyldithiocarbamate, $(C_2H_5)_2NC(S)S^-NH_4^+$ with 18C6, B18C6, DB18C6, and cryptand [2.2.2] in chloroform have been measured by means of calorimetric titrations using a Tronac Model 450 calorimeter. Solutions of the different ligands (0.018 – 0.022 mol/L) have been added continuously to solutions of the ammonium salts (0.0018 – 0.0022 mol/L). The titration time was 1 minute. Each result is the output of five independent experiments. The values of the reaction enthalpies were determined by mathematical procedures already specified in Section 1.7.3. [146, 150, 151].

During the competitive titrations a solution of the cryptand [2.2.2] (0.018-0.022 mol/l) is added to a solution of the ammonium salt (0.0018 – 0.0022 mol/L) and of the ligand 18-crown-6 (0.018 – 0.022 mol/L). Using the individual estimated reaction enthalpies for the complexation of the ammonium salts by cryptand [2.2.2] and the ligand 18C6 one can calculate the reaction enthalpy for the competitive reaction.

7.4.4 Determination of the reaction enthalpy for the complex formation between crown ethers and polar solvents in chloroform at 298.15 K

The reaction enthalpies of complex formation between crown ethers and polar solvents in chloroform were determined using the above mentioned method. To ensure that the calorimetric titration experiments between the ligand and polar solvent (water, methanol, acetone, and acetonitrile) are studied under the conditions of 1:1 complex stoichiometry the following steps have been run:

a) A solution of 18C6 ($0.02 - 0.08$ mol/L) in chloroform was titrated continuously into a solution of water ($0.01 - 0.1$ mol/L) in chloroform. Thus, the concentration of water in reaction vessel was higher compared to that of the 18-crown-6 concentration. The following reaction might occur:

$$18C6 : xH_2O,$$

where $c_{water} >> c_{18C6}$

b) A solution of water (0.02 mol/L) in chloroform was titrated into a solution of 18C6 in chloroform ($0.01 - 0.08$ mol/L). Under these conditions, the concentration of 18C6 in the reaction vessel was higher compared to that of water in chloroform. In this case, the following reaction was plausible to take place:

$$y18C6 : H_2O$$

where $c_{18C6} >> c_{water}$

Under the different experimental conditions considered above, it is obvious (within the experimental errors) that $\Delta H_1 \approx \Delta H_2$, which led to the conclusion that a 1:1 complex formation was likely to occur between 18C6 and H_2O in chloroform. To ensure the absence of any heat of mixing, a solution of ligand (0.02 – 0.08 mol/L) is titrated into pure chloroform and also, pure chloroform is titrated into a solution containing a polar solvent (water, methanol, acetone, and acetonitrile). Dependence of the strength of linear correlation between the reaction enthalpy and water concentration for complex formation between crown ethers and water in chloroform at T = 298.15 K on their cavity rings is presented in Table 10. In Figure 32 the linear correlation of the reaction enthalpy ΔH (kJ/mol) for complex formation of crown ethers with water, and water concentration in chloroform at T = 298.15 K is presented.

Futher, the reaction enthalpies of crown ethers with water in dichloromethane, 1,2-dichloroethane, and carbon tetrachloride have been measured. A solution of a ligand (0.04 – 0.08 mol/L) in dichloromethane, 1,2-dichloroethane, and carbon tetrachloride, respectively is titrated continuously into dichloromethane, 1,2-dichloroethane, and carbon tetrachloride containing amounts of water (0.03 – 0.1 mol/L).

7.4.5 Determination of reaction enthalpy for complex formation between 18C6 and alkali metal cations and ammonium salt in chloroform and different concentrations of water, methanol, acetone, and acetonitrile.

The calorimetric titrations were performed using a Tronac Model 450 calorimeter. The experiments were done at 298.15 K. The dibenzyldithiocarbamate salts of Na^+, Rb^+, and Cs^+ (0.0018 – 0.002 mol/L) obtained according to the method described in Section 7.2.1, and NH_4^+ 1-pyrrolidinedithiocarboxylate (0.0018 mol/L) are used in the calorimetric titration for determination of the enthalpy of complex formation with 18C6 (0.02 mol/L) in chloroform in the presence of different concentrations of water (0.00 – 0.04 mol/L) like in the procedure presented in Section 7.4.1.2.

The same procedure is used for the complex formation between 18C6 (0.02 mol/L) and alkali metal cations as dibenzyldithiocarbamate salts (0.0018 mol/L) in chloroform at different concentrations of methanol (0.00 – 0.098) or acetone (0.0 – 0.10 mol/L) or acetonitrile (0.0 – 0.12 mol/L) at T = 298.15 K.
The values of the reaction enthalpies were determined by mathematical procedures already specified in Section 1.7.3. [146, 150, 151].

7.4.6 Determination of complex stabilities by UV-Vis measurements

The UV-Vis spectra were recorded using a Varian Cary 5E Spectrophotometer. The absorption spectra of chloroform solution containing ligand, L_1 (1.84×10^{-5} – 2.01×10^{-3} mol/L) or L_2 (4.37×10^{-5} - 4.42×10^{-5} mol/L) and different concentrations of alkali metal cations,Li^+, Na^+, K^+, Rb^+, and Cs^+ as dibenzyldithiocarbamate salts (1.0×10^{-4} – 1.82×10^{-3} mol/L) have been recorded in the range 350 – 600 nm. The maximum of L_1 absorption is at λ = 506 nm and for L_2 at λ = 387 nm.

The stability constants of the complexes have been determined from the spectral changes of ligand in the presence of variable concentration of alkali metal cations in chloroform. The values of the stability constants have been determined by mathematical procedures already specified in Chapter 1, Section 1.7.3.3

7.4.7 Determination of complex stabilities with nearly insoluble host molecule

Complexation of potassium perchlorate with nearly insoluble ligands L_1 and L_2 in aqueous solution has been carried out [155, 156] spectrophotometrically. Stability constants were determined by measuring the increase in solubility of a nearly insoluble host due to complex formation with a soluble guest.

The solid ligand was added to solutions of the salts (2.0×10^{-3} – 2.0×10^{-2} mol/L). The amount of the solid ligand was high enough to ensure the complete saturation of the solutions. The solutions were passed through a membrane filter (polycarbonate, 0.4 μm) to remove any undissolved ligand. The UV-Vis spectra were recorded after at least 48 h, a period long enough to ensure the formation of saturated solutions. All solutions were thermostated at 298.15 K. The spectra were recorded using a Varian Cary 5 E spectrophotometer. Plotting $A/A_0 - 1$ as a function of the total salt concentration c_{salt} one expects a straight line with slope

b. From this slope, the stability constant of the complex formed in solution can be calculated using the following equation:

$$K = \frac{b}{1 - b \cdot [L]_{sat}} \tag{1.60}$$

If the solubility of the ligand is low, then the term $b[L]_{sat} << 1$, which equates to the identity between the slope *b* and the stability constant *K*. Under the experimental conditions (c_{salt} >> c_L) only the formation of 1:1 complexes will take place. The mathematical procedures of this method is specified in Chapter 1, Section 1.7.3.2.

7.4.8 Determination of stability constant and reaction enthalpy and entropy for complex formation between α-cyclodextrin and amides and nitriles

A solution of the α-cyclodextrin (0.06-0.08 mol/L) has been titrated into solutions containing the amides or nitriles ($4.0 \times 10^{-3} - 5.0 \times 10^{-3}$ mol/L) in aqueous solution.

The calorimetric titrations were performed using a Tronac Model 450 calorimeter. The experiments were done at 298.15 K.

The procedure for the calibration of the calorimeter and for the evaluation of the data has already been described in the Section 1.7.3 [146, 150, 151].

8 Summary

Taking into consideration the importance of the reaction medium upon the complex formation between ligands and cations, some aspects of the complex formation between crown ethers, cryptand [222], and α-cyclodextrin on one hand, and alkali metal cations, ammonium ion, amides, and nitriles in various media on the other hand are investigated.

First, the study of the complex formation between 18C6 and barium perchlorate and ammonium ion respectively, in mixtures of water-dioxan is performed. The water-dioxan system allows a large range of dielectric permittivity, that is, from the value corresponding to water up to the one corresponding to dioxane. Even though the ion Ba^{2+} has a higher charge than ammonium ion, the change in the water-dioxan ratio stronger influences the complex formation of ammonium ion with 18C6 rather than Ba^{2+}. The conclusion drawn from the experiments is that, besides the electrostatic interactions, hydrogen bonding interaction contributes in the case of ammonium ion, too.

In order to elucidate the effect of the medium upon the interactions involved in the complex formation, an aprotic solvent like chloroform has been employed in further experiments. Though a few salts only are soluble in chloroform, after a long series of experiments the dibenzyldithiocarbamate salts have been found to exibit enough solubility in chloroform for the proposed measurements. At low solubilities, the salts will not totally dissociate in the solvent and form ion pairs. The most important problem in nonpolar solvent arises from the existence of ion pairs because they have an influence on the complex formation between macrocyclic ligands and the cations. Throughout the experiments formation of ion pairs has been investigated. The complex formation of alkali metal cations: Na^+, K^+, Rb^+, and Cs^+ as dibenzyldithiocarbamate salts with crown ethers: 12C4, B12C4, 15C5, B15C5, DB15C5, and 18C6 in chloroform is systematically investigated by means of calorimetric titrations. The values of the stability constants, log *K*, are relatively high and the complexation is favored by enthalpic contributions. A monotonous decrease of reaction enthalpy versus cation radius for the complexation of alkali metal ions by crown ethers in chlorofrom is observed. The reaction entropy under the experimental conditions exhibits dependence on the ligand nature only. The ion-dipole interactions are responsible for the complexation behavior of crown ethers with alkali metal cations. The addition of benzo groups to the ligand (e.g., B12C4, B15C5, DB15C5) leads to a decrease in the reaction enthalpies. The reason is given by the decrease in basicity induced to the donor oxygen atoms attached to the benzene rings. As a result, the strength of the interaction is reduced. The reaction entropies decrease also when a benzo group is attached to the ligand (e.g., B12C4 and B15C5). This is due the ligand rigidity that rises by addition of benzo groups that gradually decreases the ligand flexibility. When a second benzo group is added, the value of the reaction entropy continues to decrease by about the same amount (e.g., DB15C5).

The reaction enthalpies for complex formation of ammonium salts with [2.2.2] cryptand are higher compared to the corresponding values for complex formation of ammonium salts with the ligands 18C6, B18C6, and DB18C6 in chloroform. This is due to the complete encapsulation of ammonium ion by the ligand [2.2.2]. The enthalpy of complex formation between ammonium salts and crown ethers is influenced by the presence of the benzo group attached to the ligand (e.g., B18C6 and DB18C6). The nature of the anion borne by the ammonium ion has a significant influence on the complexation of ammonium by ligands. In this respect, competitive reactions are carried out. In contrast, the experimental values of the reaction enthalpy ΔH_{comp} (experimental) for the competitive reaction of the ammonium salt

complexes with 18C6 by the [2.2.2] cryptand in chloroform and 1,2-dichloroethane show no significant influence of the anion. Thus, the ion pair obviously dissociate during the formation of the preformed complex. In order to validate this observation, more experiments are carried out in dichloromethane and dioxane; all obtained results prove the supposition made. The influence of solvent (like chloroform, 1-2 dichloroethane, dichloromethane and dioxan) on the reaction enthalpy of the complex formation between ammonium salts with crown ethers and [2.2.2] cryptand is also studied. The results indicate that the value of the reaction enthalpy for the complex formation of ammonium diethyldithiocarbamate with [2.2.2] cryptand obtained in 1,2-dichloroethane is equal the one obtained in chloroform. In this case, the ion pair obviously dissociates during the complete encapsulation of the ammonium cation into the [2.2.2] cryptand and no difference in solvation of the salt, ligand and complexes occurs.

Further, the interest is focused on the influence of adding small quantities of polar solvent (like water) to chloroform. The interactions between crown ethers and water molecules in chloroform are studied. The results reveal the formation of a 1:1 complex between crown ethers and water in chloroform. The hydrogen bonding and ion-dipole interactions are responsible for the complex formation between water molecules and the crown ethers. The obtained values of the reaction enthalpies for the complex formation between 18C6 and water in chloroform at different concentrations of water depend on the water concentration and are not influenced by the use of various concentrations of 18C6. The reaction enthalpy of complex formation between 12C4, 15C5, and B18C6 and water in chloroform shows a trend to decrease correlated with the decrease in the ring size of the crown ether. As expected, the value of the reaction enthalpy for the complex formation between B18C6 and water in chloroform is smaller than the one obtained in the reaction of 18C6 and water in chloroform.

Following the same goal of getting more information about the influence of the reaction medium on the complexation between 18C6 and water, chloroform is replaced by: dichloromethane, 1,2-dichloroethane, and carbon tetrachloride. For the reaction of 18C6 with water in all the above mentioned halogenated solvents, the value of the reaction enthalpy of the complex formation between 18C6 and water decreases in the following order: carbon tetrachloride > dichloromethane > 1,2-dichloroethane.

Since the hydrogen bonds are responsible for the complex formation between 18C6 and water in chloroform, further investigations have been performed by replacing water by methanol, which has one hydrogen eligible to interact with the ligand, rather than two hydrogens in the case of water. The reaction enthalpy remains constant for methanol concentrations within the range $[0.0 - 0.1]$ mol/L, whereas a significant change occurs at concentrations higher than 0.1 mol/L. In the range, where there is no significant change in the reaction enthalpy for the complex formation between 18C6 and methanol in chloroform due to methanol concentration, it is likely that a homogeneous mixture between the complex of 18C6 with methanol and chloroform exist. A possible explanation for the increase in the reaction enthalpy at higher methanol concentration resides in the formation of small methanol clusters within chloroform.

When using acetone instead of methanol, there are no significant values of the reaction enthalpy for the complex formation with 18C6. This may be caused by the absence of any hydrogen bonding between acetone and 18C6. Likewise, there is no noticeable effect on the reaction enthalpy for the complex formation between 18C6 and acetonitrile in chloroform.

Once the influence of the polar solvents solely upon ligands in chloroform has been investigated, the focus of attention is laid on the reaction of crown ethers with cations in nonploalar medium with small amounts of polar solvents added. The aim is to get deeper

insight into the solvation (hydration) of the salts. A linear dependence of the reaction enthalpy on the cation radius for the complex formation between 18C6 and alkali metal cations as dibenzyldithiocarbamate salts in chloroform in the presence of water suggests a predominant ion-dipole interaction. Also, the results clearly indicate that the complex formation of NH_4^+ with 18C6 in chloroform is not influenced by the presence of water. In the case of methanol instead of water, a correlation between the cation radius and the influence of methanol on the complex formation between 18C6 and alkali metal as dibenzyldithiocarbamate salts in chloroform is also observed. The dependence of the reaction enthalpy on the cation radius for the reaction between 18C6 and alkali metal dibenzyldithiocarbamate salts in chloroform in the presence of methanol suggests that the nature of interactions is not predominantely electrostatic due to a significant deviation from linearity.

The variation of the reaction enthalpy is very small or within the experimental errors for the complex formation of 18C6 with Na^+, K^+ , Rb^+, and Cs^+ as dibenzyldithiocarbamate salts in chloroform at different concentrations of acetone ($0.0 - 0.10$ mol/L).

The experiments so far have been carried out by calorimetric titration. In order to double check the results, a new set of experiments has been performed by a spectrophotometric method. The stability constant of the complexes formed between an aza-15-crown-5 derivative, L_1 3-[4-(1-aza-15-crown-5)-phenylazo]phthalhydrazide and Li^+, Na^+, K^+, Rb^+, and Cs^+ as dibenzyldithiocarbamate salts in chloroform is determined based on the spectral changes of the ligands in the presence of variable concentration of alkali metal cations in chloroform. The values of the stability constants of the complexes increase with the cation radius. A benzo-15-crown-5 derivative, N(benzo-15-crown-5)-3,5-dinitroanthranilic acid forms complexes with the alkali metal dibenzyldithiocarbamates in chloroform having the values of stability constants quite similar. Hence this ligand does not exhibit selectivity for the alkali metal cations. The wavelength of maximum absorbance, λ_{max} , of the absorbing complex formed between N(benzo-15-crown-5)-3,5-dinitroanthranilic acid and alkali metal ions at different concentration is shifted towards higher wavelengths (i.e., bathochromatic effect) as compared with the spectral behavior of the free ligand ($\lambda_{max} = 387$ nm). The solubilities of the ligands L_1 3-[4-(1-aza-15-crown-5)-phenylazo]phthalhydrazide N(benzo-15-crown-5)-3,5-dinitroanthranilic acid are obtained from the measurements of the TOC values as a function of the total salt concentration.

Further, the complex formation of α-cyclodextrin with uncharged guests, such as amides and nitriles, respectively, in aqueous solution has been investigated by calorimetric titration. The results demonstrate the influence of solvation changes during the complex formation of uncharged molecules with α-cyclodextrin.

The complex formation of α-cyclodextrin with amides and nitriles depends on the release of water molecules from the cavity of α-cyclodextrin. The complex formation between crown ethers and alkali metal cations, where the reaction enthalpy decreases and the entropy increases with the increase in the cation radius, is governed by the enthalpic contributions. Instead, the entropic contributions are responsible for the complex formation between the uncharged host and guest molecules, especially for the complex formation of α-cyclodextrin with amides and nitriles.

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