

Review Paper

A Review of the Thermodynamics of Complexation of Crown Ethers With Metal Ion



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ABSTRACT

Recently, macrocyclic and supramolecular chemistry has reached a hopeful area of research in the mutual interaction between chemistry, physics and biology. Charles J. Pedersen, at du Pont figure out a compound in the early 1960s famous for dibenzo-18-crown-6 (DB18C6) later on. The detection of the complex formation in solution, the designation of the stability of the consequence complex or complexes and the determination of the thermodynamic or the kinetic parameters of the complex formation can be attained by a manifold of physicochemical measurements. Conformational rigidity or flexibility of macrocycles has a considerable penetration on their selective behavior. The number, type, and arrangement of donor atoms in the macrocyclic rings play a main role in macrocycle selectivity. Based on chemistry terminology, this is known as “host-guest” chemistry where the ether plays the role as the host and the ionic species as the guest. In organic solutions, crown ethers take the role of phase-transfer catalysts and agents in order to enhance the solubility of inorganic salts. Macrocycles need to compete with solvent molecules for the cations during the process of complexation. Consequently, variation of the solvent makes a considerable change in the manifest binding characteristics of these ligands.

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1. History

The first macrocyclic polyethers were introduced by Luthringhaus in 1937 as part of research of intermediate and large size [1]. However, the significance of these compounds began from 1967 with the discovery of dibenzo-18-crown-6 (DB18C6) by Pedersen and he observed that this compound and similar homologues form stable complexes with alkali and alkaline earth metal ions [2]. Moreover, Pedersen managed to develop more than 60 compounds of this family so as to determine the optimized ring size and preferable conditional arrangement of oxygen atoms in the macrocycles [3]. He also studied the ability of these compounds in the complexation with a variety of cationic species. It was found that crown ethers, including between five and 10 oxygen atoms, have the highest complexing power. Soon after Pedersen's publications in 1967 [2, 3], Lehn and his co-workers in Strasbourg, France, introduced new macrobicyclic ligands called "cryptands" [4].

Recently, macrocyclic and supramolecular chemistry have reached a hopeful area of research in the mutual interaction between chemistry, physics and biology. Charles J. Pedersen at du Pont figure out a compound in the early 1960s, known as dibenzo-18-crown-6 (DB18C6) later on. Pedersen was trying to develop a significantly varied compound, since he isolated DB18C6 from a "brownish goo" in a 0.4% yield. Pederson knew well that something important was about to take place when his latter characterization of the colorless, crystalline byproduct indicated that Na^+ made it be solubilized in methanol and that its molecular weight was doubled that of benzo-9-crown-3 (B9C3). Knowing that he had something weird, Pederson [5] devoted all his energy to deal with this appealing category of ligands through synthesizing a great diversity of macrocyclic polyethers and determining their interplay with inorganic cations. This effort was fruitful and a monumental paper was published by Pedersen in 1967. His paper immediately absorbed the consideration and fondness of a great number of scientists globally. During the next decade there happened a revolution in the number of laboratories, therefore, an enormous number of research led to the synthesis and characterization of a large number of innovative macrocyclic chemical structures as well as their application in various fields. This effort covered many fields including structure analysis, phase transfer catalysis, biochemistry and ion transport in membranes, and organic and inorganic synthesis. Generally, one of prominent features of this innovative growing field in macrocyclic chemistry was

its focus on the high selectivity, that host macrocycles had for a diversity of guest compounds.

The first synthesis of macrocyclic polyethers including three polyether stands joined by two bridgehead nitrogens were reported by Dietrich [5], and were used as ligands. The compounds have three dimensional cavities, and called 2-cryptands (where, 2-indicates a bicyclic ligand). Identical ligands that contain three and four macrocycles including 3-cryptands and 4-cryptands respectively have been also synthesized [6].

Cryptand and crown ligands have been prepared in which some or all of the etheric-oxygen atoms were replaced by sulfur or nitrogen atoms. Such substitutions had modified the complexing abilities of the ligands. The thia- and the aza- derivatives of the crown ethers have considerable interests with regard to their complexation attributes in solution. The thia- and the aza- derivatives of the crown ethers have noticeable interests, not only with alkalis, but also with other bivalent and univalent metal ions and the replacement protonated amines as well [7].

2. Types of Macrocyclic Polyether

Initially, Pedersen [3] was able to synthesize over fifty cyclic polyethers (crown ethers), having the ring size ranging from 9 to 60 atoms (in which 3 - 20 were oxygen atoms). He confirmed that a number of these compounds indicated to have a considerable selectivity towards certain alkali metal ions, which reminded the behavior of certain antibiotics [8].

The discovery [2, 3, 9] that anions and cations form stable complexes with polyamines and macrocyclic polyethers has been a significant achievement in the world of chemistry. Scientists were more interested in these macrocycles when they discovered that some of them formed stable complexes with alkaline earth and alkali metal ions and that they reached preferential cation complexation through matching the sizes of ligand cavity and the cation relatively [10].

The relative large tendency of some of these cyclic polyethers for ions of alkali metal were totally unpredicted because ethers are not commonly considered to be good complexing agents, unless there are very strong Lewis acids. Moreover, his primary observation that macrocyclic polyethers have indicated to be strongly complexed with plenty cations besides the alkali metal ions (e.g. Ba^{2+} , Ag^+ , Hg^{2+} , Pb^{2+} , ...) in water was real. Many additional polyethers (in minor polar solvents) were reported by Frensdorff [11] and Haymore [12].

Furthermore, these synthetic ligands have structures and reactions similar to many compounds of the macrocyclic type that occur naturally and are famous for the exhibition of selective cation complexation [13]. The study of many of these ligands have been challenging in expounding the cation and anion binding data with regard to the observed selectivities and solvation properties of the ligands under various empirical conditions. Pedersen, Cram and Lehn, 1987 Nobel Prize winners, pointed out that this field leads to complicated basic features of molecular cognition and self-organization and applies biological principles in designing smart artificial systems. Accordingly, this field has an incredible potential for future use in subfields like bio and nanotechnology, environmental protection, molecular electronics, catalysis, medicine, and photonics.

3. Recent Publications

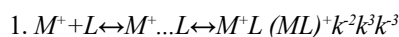
Macrocyclic Polyethers were used for many applications on both scientific and applied fields in chemistry. Preferred solvation of silver (I) cryptand 2, 2, 2-perchlorate complexes in acetonitrile- water and acetonitrile mixtures- methanol were carefully studied by Kalidas et al. [14]. Ion-pairing were studied by Krienke and Barthel [15] and Deepa [16] to explain the ion-solvent interactions using different electrolytes and studying also ion solvent polymer interactions by using conductivity, relaxation and FT-IR measurements. Studying the solute-solvent and solute-solute interactions are very important in chemistry, like the interaction dibenzo-24-crown-8 with some alkali metal picrate by extraction method was studied by Takeda et al. [17]. Also, studying ionic solvations in polar supercritical fluids is important like the work done by Kapko and Egorov et al. [18]. Thermodynamics of complexation of aqueous 18-crown-6 with sodium and barium ions were studied by Brown et al. [19] by the use of the apparent molar heat capacities and apparent molar volumes at different temperatures. Studies of the anion solvation is important like the work done by Fawcett et al. [20] on the anion solvation in polar-aprotic solvents to give complete illustration about the electrolyte solvation. Recently, Raman spectroscopy was used by Alia et al. [21] for studying the preferential solvation and ionic solvation such as studying some lithium and silver electrolytes solvation in mixed acrylonitrile-dimethylsulphoxide solutions. A number of other recent researches in this area have been cited in the references: [22-28].

4. General Considerations of Macrocyclic Polyethers Complexes for Complexes Formation in Solutions

The detection of the complex formation in solution, the designation of the stability of the consequences complex or complexes and the designation of the thermodynamic (entropy, enthalpy) or the kinetic parameters of the complex formation can be attained by a variety of physico-chemical measurements. Several texts define these techniques in significant details [29]. There are plenty of factors affecting the formation of crown ether complexes of metal ions in solutions from which cation diameter-crown's cavity size ratio can be accounted on as the most emphasized one; however, its role against large crown ethers has been questioned [30]. Having highly flexible geometries, large crowns (e.g. larger than 18-crown-6) adapt their conformations for optimized complexation of guest titles. Therefore, the formation of "wrap-around" complexes between some alkali metal ions and crown ethers both in solid state [31] and solution [32], are expected. The numeral and the nature of heteroatoms participating in bind of cation, the nature of substituted groups on the macrocyclic ring, and especially, the solvent properties are of some other important factors [30]. The solvent nature itself can incredibly affect the selectivity, stoichiometry, exchange kinetics and thermodynamic stability of crown ether-metal ion complexes [30].

5. Complexation Processes

In utmost cases, crown ether- metal cation complexation processes can be explained with the multistep Eigen-Winkler mechanism (Equation 1): [33].



where, L=free macrocyclic ligand, M^+ =solvated metal ion, $M^+ \dots L$ solvent-separated macrocyclic ligand- metal pair, M^+L =contact pair, $(ML)^+$ =final complex with the metal cation embedded in the cavity of macrocyclic. Ratio of Mn^+ : 18C6 cavity Radii. The Eigen-Winkler mechanism includes a hierarchy of stages in which both crown ethers and solvent may affect the activation energy specifications of the process for the same metal cation. Macrocyclic ligand and partial cation desolvation are partially rearranged in the first stage. In the next stage, the metal ion is encircled and encapsulated and desolvation becomes rather complete. The rate determining step of the final process can be desolvation H_2O or ligand rearrangement (such as MeOH or DMF), depend-

ing on the relative energy of desolvation compared to the energy of ligand rearrangement [34]. In low dielectric constant solvents, the ion pair from the substrate is attacked by the crown ether.

6. Conformational Rigidity or Flexibility

It is proved that flexibility or rigidity of macrocycles has a massive effect on their selective behavior. "Rigid" type macrocycles such as those mentioned above distinguish between cations that are larger and smaller than optimally sized cations (peak selectivity). "Flexible" types of macrocycles mainly distinguish small cations (plateau selectivity) [35].

7. Kind, Arrangement, and Number of Donor Atoms

Also, the number, arrangement and type of donor atoms in the macrocycle play an important role in the selectivity of macrocycles. The oxygen donor atom of crown ether has the highest affinity for alkalis, alkaline earths, and lanthanide ions. Nitrogen donor atoms support transition metal ions. Sulfur donor atoms interaction preferentially with Ag^+ , Pb^{2+} , and Hg^{2+} [36]. The tertiary amine nitrogen donor atom forms a more stable complex with Ag^+ than the secondary amine nitrogen donor atom [37]. Replacing the nitrogen atom of the large cyclic ring with an oxygen atom has a significant effect on both the kinetics of the complex reaction (faster reaction rate) and the stability constant of the complex with the transition metal ion (decreased stability) [38, 39].

8. Host-guest chemistry

Characteristic chemistries of crown ethers include the complexation of ether oxygen with various ionic kinds. This is known as "host-guest" chemistry, where the ionic species is the guest and the ether is the host. Crown ethers can be used as phase transfer catalysts and as agents to meliorate the solubility of inorganic salts in organic solvents.

For instance, "Purple Benzene" is a solution of 18-Crown-6, benzene, and potassium permanganate used as oxidants. Crown ether dissolves in benzene, potassium ions form a complex with crown ether, and permanganate is forcibly dissolved in benzene to form an ion pair with potassium ion. Owing to the presence of lone pairs of electrons, oxygen atoms can function as Lewis bases (for example, hydrogen bonds between water molecules and hydration of metal ions in aqueous solution.

18-crown-6, complex hydration of a metal ion Takeda et al. [40] in 1980 studied the complex formation reactions between alkali metal ions and 15-crown-5, 18-crown-5 and dibenzo-24crown-8 in propylene carbonate by means a conductometric method. They observed that the K_{ML^+} value for the complex of the same alkali metal ion with crown ether varies in the order $18C6 > DB24C8 > 15C5$ and the stability subsequences of the alkali metal ions with 15C5, 18C6 and DB24C8 are $\text{Li}^+ > \text{Na}^+ > \text{K}^+ > \text{Rb}^+ > \text{Cs}^+$, $\text{K}^+ > \text{Rb}^+ > \text{Cs}^+$ and $\text{Na}^+ > \text{K}^+ > \text{Rb}^+ \geq \text{Cs}^+$, respectively.

In 1987, Zollinger et al. [41] investigated the stability constants and the stoichiometries between crown ethers 15C5, 18C6, DC18C6 and DB24C8 and divalent cations Ca^{2+} , Ni^{2+} , Zn^{2+} , Pb^{2+} , Mg^{2+} , Co^{2+} and Cu^{2+} in methanol solution by the conductometric and polarographic techniques. They found that LogK of 1: 1 complexes are generally in the range of 2.1-4.2, which is low in comparison to that of the corresponding crown ether alkali metal ion complexes. They observed M2L complexes for the systems $\text{Pb}^{2+}/18C6$, $\text{Pb}^{2+}/DC18C6$ and $\text{Cu}^{2+}/DB18C6$, whereas ML2 complexes were found for $\text{Ca}^{2+}/18C6$ and $\text{Cu}^{2+}/18C6$. They did not observe any obvious relationship between hole size of ligand and cation diameter.

Tawarah and Mizyed [42, 43] in 1988 obtained the thermodynamic parameters for complexation reactions between benzo-15crown-5 and dicyclohexano-18-crown-6 and alkali cations Na^+ , K^+ , Rb^+ , and Cs^+ in acetonitrile solutions at 308, 303, 298, 293 and 288 K using a conductometric technique. They used a nonlinear least squares curve fitting procedure in order to determination the limiting molar conductance and the stability constant of the resulting 1: 1 complexes from the molar conductance-mole ratio data. Based on the value of Log K at 298K, they observed the binding sequences for DC18C6 and B15C5 complexes as $\text{K}^+ > \text{Na}^+ > \text{Rb}^+ > \text{Cs}^+$ and $\text{Na}^+ > \text{K}^+ > \text{Rb}^+ > \text{Cs}^+$, respectively.

Lee et al. [44], in 1990 studied the complexation of 18-crown-6 (18C6) and 1,10-dithio-18-crown-6 (DT18C6) with univalent cations (K^+ , Ag^+ , Tl^+ and NH_4^+) in methanol at different temperatures using a conductometric technique. They also reported the changes of the entropy and enthalpy values for the complexation reactions. In this study, the selectivity order of 18C6 was $\text{K}^+ > \text{Tl}^+ > \text{Ag}^+ > \text{NH}_4^+$ while that of DT18C6 was $\text{Ag}^+ > \text{Tl}^+ > \text{NH}_4^+ > \text{K}^+$. The results showed that by sulfur substitutions in 18C6, the stability constants of DT18C6- M^+ (except Ag^+) decreased significantly due to the weak "hard acid-soft base" interactions and the decreased cavity sizes. They also

described the increase in stability constant of DT18C6-Ag⁺ complex by soft-soft interaction between silver ion and sulfur centers. Amini and Shamsipur [45] in 1991 studied the complexation reactions between dibenzo-30-crown-10 and Li⁺, Na⁺, K⁺, Rb⁺, Cs⁺, Ag⁺ and Tl⁺ ions in nitromethane, 1,2-dichloroethane, acetone, acetonitrile and dimethyl formamide solutions at 25°C by means of a conductometric method. In his study, stability constants of the resulting 1:1 complexes were determined and found to decrease in the ordering Tl⁺>Rb⁺>K⁺>Ag⁺>Cs⁺>Na⁺>Li⁺. They also observed an inversely proportional relationship between solvent Gutman Donicity and complex stability. The data obtained in this perusal confirmed the existence of a “wraparound” structure of the upper complex in solution.

Jabbari et al. [46] in 1993 studied the complexation reactions between Ag⁺ and Tl⁺ and DA18C6, DC18C6, DB30C10, 18C6, DB21C7, DB24C8, DB18C6, B15C5 and 12C4 in aceto nitrile, acetone, and dimethyl formamide at 25°C by using a conductometric technique. They determined the stability constants of the resulting 1:1 complexes and found to decrease in the ordering DA18C6>DC18C6>DB30C10>18C6>DB21C7>DB24C8>DB18C6>B15C5>12C4 in the case of Tl⁺ complexes and in ordering DA18C6>DC18C6>18C6>DB18C6>DB24C8>DB30C10>B15C5>DB21C7 for Ag⁺ complexes. In this study, they observed a reverse relationship between the Gutmann Donicity of the solvents and the stabilities of the complexes. They also discussed the influence of the number of atoms in the macrocycle and of substitution in the polyether ring on the stability of the complexes. Salomon and Hefter [47] in 1993 offered a method of conductometric for precise determination of the formation constants between 18C6 alkali and metal cations in 2-cyano pyridine solvent at 30°C. Their procedure also permit accurate assessment of association equilibrium constants between the complex species the anion and (M-18C6)⁺.

Hasani and Shamsipur [48] in 1994 studied the interaction between ammonium ion and DC18C6, 18C6, DB30C10, DB21C7, DB24C8, DB18C6 and B15C5 in acetonitrile solution at different temperatures conductometrically. They obtained the stability constants of consecutive 1:1 complexes at various temperatures from the molar conductance-mole ratio data and found to vary in the ordering DC18C6>18C6>DB30C10>DB21C7>DB24C8>DB18C6>B15C5.

9. Relative Ligand Cavity and Size of Cation

From the crown ethers investigation, it was recognized that these ligand complexes were mostly stronger than that metal ions whose ionic crystal radius were best matched the radius of the ring cavity [3]. The metal ions will fall through the cavity if the macrocyclic ring is too big (in the simplistic picture it can be considered that the ligand to be inflexible) but, if the macrocyclic ring is tiny, the metal ion can only saddle up to it, not fit in-trant [49]. It is observed from a previous data that the maximum stability for the complexes of 18C6 with both the alkaline earth cations and the alkali metal occurs at a metal ion to cavity diameter ratio of unity.

10. Number of Donor Atoms

Cram et al. [50] reported that 18C5 crown ether was a much poorer host for t-butyl ammonium ion than 18C6 crown ether. Also, in the reaction of thia-substituted crowns with Hg⁺ and Ag⁺, the increase in complex stability was associated with the increment in number of the sulfur atoms in the ring.

11. Substitution in the Macrocyclic Ring

The effect of the substitutions in the macrocyclic ring was observed in comparing 18C6 to DB18C6 crown ethers. In methanol as a solvent, the formation constant of the Ba²⁺ complex of 18C6 was bigger than that of K⁺ complex by a coefficient of 10. On the other hand, dibenzo-18-crown-6 displayed the contrary preference binding of K⁺ rather than Ba²⁺ in methanol by almost the same amount. These results were explained by the bulkiness of the ligand lead to separation of the cations from the solvent. It can also be theorized that the aromatic ring gives the ligand rigidity and abstracts electrons from the basic oxygen donor, reducing the solidity of the metal-ligand action and reaction. Substitution of cyclohexane with a benzoyl group in crown ethers did not have a meaningful effect on the stability or cation selectivity of the complex.

Shchori et al [29] showed that the dinitro derivative of DB18C6 crown ether had specifically reduced affinity for Na⁺ as compared with the not replaced ligand in DMF as a solvent. This was consistent with the electron withdrawing character of the -NO₂ substituents, which may delocalize the electrons from the oxygen donors. Conversely, substitution by -NH₂ resulted in a small growth in the complex stability constant.

12. Type of Solvents

When complexed, macrocycles should compete with solvent molecules for cations in solution. Consequently, changing solvents can result in considerable changes in the apparent binding attributes of these ligands. In particular, low dielectric constant and soluble solvents have higher complex stability than solvents that tend towards strong cationic solvation. In addition, the reaction medium is the main reason for some cations to be selected over other cations. Izatt et al. [51, 52] studied the reaction of 18C6 crown ethers with cations in methanol / water solvents of different compositions. The obtained results defend the findings of Kaufman et al. [53] that the increased stability of methanol to water is primarily of enthalpic origin. Actually, both studies reported that the reaction entropies actually opposed this enhancement. Agostiano et al. [54] studied the reactions of DC18C6 crown ether with alkali metal ions in ether in three alcohols of consecutively bigger carbon chain length; (n-propanol, ethanol and methanol). Their results are demonstrated that while the ligand was selective for K^+ over Na^+ and Cs^+ , the selectivity between Cs^+ and Na^+ reversed over the range of solvents studied. Changes in the selectivity were also observed for the complexation of DB18C6 crown ether with alkali metal ions among the solvents [55] (MeOH, DMF and DMSO). Many methods are widely used to study the dynamics and thermodynamics of the complexing of multiple crown ethers in multiple aqueous solvents and solvent mixtures. Such as Mass spectrometry [56], UV spectroscopy [57], electrochemistry [58] and calorimetric study [59]. However, in previous studies, NMR spectroscopy was widely used as a potent technique for studying the dynamics and thermodynamics of crown ether complex formation in non-aqueous solvents [60].

Solutes and solvents can be widely divided into non-polar and polar. There are many agents that explain the attributes of a solvent. Polarity could be measured as the permittivity of a compound or the dipole moment. Polar solvents can be further divided into polar aprotic solvents (such as methanol and water) and polar protic solvents (such as acetone, aceto nitrile, dimethyl formamide, and dimethyl sulfoxide). Donor number (DN) is a qualitative scale of basicity of Lewis. It is defined as the negative enthalpy value for 1:1 adduct formation between the standard Lewis acid $SbCl_5$ and a Lewis base, in dilute solution in the non-coordinating solvent 1, 2-dichloroethane with a (zero,0) DN. The Donor number represents the ability of the solvent to solvate the cations and Lewis acid. This method was expanded by Gutmann in 1976 [61]. Solvents undergo a variety of

weakness chemical interactions with solutes. The most common actions and reactions are relatively weakness van der Waals actions and reactions (induced dipole actions and reactions), stronger dipole-dipole actions and reactions, and even more powerful hydrogen bonds. The role of solvents in organometallic substitution reactions could not be exaggerated. Even minor changes in solvent structure can result in significant changes in the speed and pattern of processes in solution [61].

13. Solvation

In most of the solution (dilution), each solute (molecule or ion) is covered by a big number of solvent molecules. Solvation regarding to the energy interaction (solute-solvent interaction) that occurs between the solute and the entire solvent molecule that surrounds it.

Solvation energy is defined as the energy required for the process of moving the molecules of dissolved ions from their separated state in vacuum to most of the solvent. Thermodynamics allow this energy to take the Gibbs free energy G . This is believed to be characteristic of redemption [62]. The investigation of dissolving solvents, including electrolytes, has long been a topic of interest to solution chemists. Thus, studies on the transport properties of electrolytes in non-aqueous and aqueous solvents are of interest for a variety of technologies such as photoelectrochemical batteries, high energy density batteries, wet electrolytic capacitors, electrodeposition, and electro-organic synthesis. Ion solvation is a charming area of chemistry, since solvated ions are ubiquitous on earth hydrated ions arise in aqueous solution in lots of organic and chemical systems. Ions solvated in natural solvents or combos of natural solvents and water also are lot prevalent. Selective solvation takes place when the solvate takes precedence over one solvent over the other solvent. This is a phenomenon and it could be applied to separate different ions from each other, a procedure known as solvent separation. The exchange of solvent molecules of ions in solution is the basis for perception the reactivity of ions in solution. Solvated ions also play an important impress in electrochemical applications. For example, the conductance of an electrolyte depends on the interaction of ions and solvents [63].

One of the fundamental questions in running a chemical process in solution is the control of process parameters. Most significant are the yield and process rate of the reaction product [64]. The rate constants and equilibrium of processes in solution are multifactorial dependent. In other words, they depend on many solvent properties and temperature. Running the process with

individual solvents mostly makes such control difficult, and in some cases absolutely impractical. Meanwhile, it is feasible to select properties that directly determine the process behavior in the mixed solvent. These properties are primarily related to density, viscosity, permittivity, and specific solvation energy. The application of blended solvents in industrial and scientific practice began in the early 20th century. However, principled theoretic experimental research started in the 1960s and has been increasing in intensity since that time. There are two fundamental explanations for the physical attributes of blended solvents. One is the reference version of Volume 4 of Timmermans [65], which was later voiced by Krestov [66].

14. Applications of Crown Ethers

Due to their selective complex formation with hard metal ions and negligible water solubility, crown ethers are widely used as appropriate ion carriers in solid-phase and solvent-solvent extraction [67], ion transport [68], ion-selective and PVC membrane ion-selective electrodes scrutinies [69] and crown ether complexes, used as nano switches lately [70].

Crown ethers have widely been scrutinized in parallel with naturally occurring ion-selective cyclic antibiotics such as enniatin and valinomycin, and are simple models to describe the mechanisms of transport and neurotransmission of these biologically related cations. Acts as a model [71]. In addition, studies of crown ether toxicity have shown that the compound is not genetically toxic, despite cytotoxicity in mammalian cells, but it is highly toxic in prokaryotes and eukaryotes [72].

Some chiral derivatives of the crowns were able to differentiate between enantiomers of optically active species, making them of specific biological interest [40-55, 73]. For example a review, with 18 references, discussing the structure and properties of crown ethers, especially with respect to their use in medical diagnosis and therapy was reported [74]. Their privilege to form metal ions complexes made them useful as carriers for radio-nuclides in tumor radiotherapy. The insecticidal activity [75] of new derivatives of dibenzo-18-crown-6 and the toxicologic characteristics [76] of the crown ethers (DB18C6 and diaza-18C6) were also studied. Crown ethers in nuclear energy, electronics and electrochemical, photosensitive materials, and military [77]. In that study, they investigated the effect of temperature on the electrochemical activity of graphite electrodes in a 20-80°C co-insertion reaction in a sodium cell [78]. The separation of Li^+ , Na^+ , K^+ , Ca^{2+} , Cs^+ , Ba^{2+} organic and

inorganic substances was studied in presence of crown ethers (12C4, DB18C6, 18C6 and DC18C6) using chromatographic extraction technique [79]. Morrison et al. investigated 18C6, 15C5, and 12C4 for their ability to enhance solubility of ocular drugs and increase their penetration into the cornea [80]; crown ethers were used as a phase-transfer catalysts via complexation or solvation of the inorganic cations; changing their properties thus generated lipophilicities. Also, crown ethers were used as polymer supported phase-transfer catalysts offering the following advantages commonly with heterogeneous catalysts [81].

Ethical Considerations

Compliance with ethical guidelines

Ethical issues including misconduct, informed consent, plagiarism, fabrication and/or data falsification, submission and/or double publication, and redundancies were utterly observed by the author.

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Conflict of interest

The authors declare no conflict of interest.

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